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THE GENESIS OF ATHEROSCLEROSIS

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The occurrence of fatty material in the lesions of the commonest form of arteriosclerosis was believed by Virchow [1] to be due to a fatty degeneration following a primary inflammatory overgrowth of the intimal connective tissue. This overgrowth resulted from mechanical irritation of the intima by the pressure of the blood at critical points. The thickening of the intima by this overgrowth interfered with the nutrition of the intimal cells, which depend for their sustenance on imbibition of plasma from the blood circulating in the arterial lumen. Fatty degeneration was a natural consequence. Marchand [2] characterized the form of sclerosis combining sclerotic and fatty changes as "atherosclerosis." Aschoff,[3] working with Adami, discovered that the fatty material in the diseased portions of arteries was made up largely of cholesterol esters.

Aschoff revived the Virchow theory in modified form, expressing his concept of the process as follows:

> The functional wear and tear or excessive stresses cause a loosening of the ground substance of certain systems together with proliferation of other systems. The entering blood plasma renders apparent the functional deterioration, more or less clearly, according to its content of cholesterol esters or of calcium. In this manner it makes visible the fact that deterioration has occurred and by chemical changes and necrosis advances to the formation of calcified plates or ulcerations, which form the end links in a continuous chain of one and the same process.

The swelling of the ground substance begins in the deep layers of the intima and is accompanied by molecular disintegration. The deposit of lipoids is mechanical and limited to the intercellular spaces.[4]

From the Medical Examiner Service of Suffolk County.

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1. Virchow, R.: Phlogose und Thrombose in Gefäss-system, in Gesammelte Abhandlungen zur wissenschaftlichen Medizin, Frankfurt, F. Meidinger Sohn & Co., 1856.

2. Marchand, F.: Ueber Arteriosklerose (Athero-Sklerose), Verhandl. d. Kong. f. inn. Med. **21**:23, 1904.

3. Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch. **10**:106, 1907.

4. Aschoff, L.: Arteriosklerose, Med. Klin., 1914, supp. 1, vol. 10.

Anitschkow and Chalatow,[5] after the dietary experiments of the Russian school with fatty foods, succeeded in producing atherosclerosis in rabbits by feeding them pure cholesterol in oil.

Investigators have tended to adopt the Aschoff theory of mechanical infiltration of the intercellular spaces by plasma as the source of the lipoid substances. Anitschkow,[6] nevertheless, could not agree that the primary process was degenerative.

> The primary lipoid infiltration of the arterial wall gives rise to a secondary reactive hyperplasia of the fibrous-elastic elements, resulting in the formation of typical sclerosis plaques of a connective tissue character. . . . The whole morphologic picture of the lipoidal accumulations contradicts that idea [of primary degeneration]. The normal structure of the arterial wall remains unimpaired after the lipoidal substances have made their appearances.

Duff[7] accepted the theory of lipoid infiltration of the intercellular spaces in experimental atherosclerosis but believed that injury to the vessel wall, due to the presence of large quantities of cholesterol in the blood, was an essential primary factor leading to intercellular precipitation of the cholesterol.

Klotz,[8] however, maintained that in human lesions in the early stage the lipoid was intracellular.

> Free fat is not seen in any part of the intima, and no evidence is at hand to indicate that the fat is deposited by a mechanical process, as was suggested by Ribbert and Aschoff.

Klotz[9] expressed the opinion that erroneous observations in this respect arose from study of advanced lesions and issued his famous dictum on the subject: "A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions." He found that the fat was contained in "endothelial-like cells (lutein-like cells)" in early lesions and asserted that the relation of this fatty material to the subsequent development of atheroma was obvious.

The debatable questions in the studies cited are two: 1. Is the introduction of lipoid into the subendothelial layer of the intima a primary or a secondary process? 2. Is the lipoid free or contained within cells?

It is customary with reference to human atherosclerotic lesions to select for microscopic study visible lesions. If early lesions are to be studied, those are sought which are small and colored orange or yellow, i. e., lesions which are rich in lipoids. The least advanced of these visible lesions have been looked on as primary. Of course, the primary lesion

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5. Anitschkow, N., and Chalatow, S.: Centralbl. f. allg. Path. u. path. Anat. **24**:1, 1913.

6. Anitschkow, N., in Cowdry, E. V.: Arteriosclerosis: A Review of the Problem, New York, The Macmillan Company, 1933.

7. Duff, G. L.: Arch. Path. **20**:81 and 259, 1935.

8. Klotz, O.: J. M. Research **32**:27, 1915.

9. Klotz, O.: J. M. Research **31**:409, 1915.

of atherosclerosis is not grossly visible. Its discovery is a more or less unexpected microscopic observation by a careful worker who is seeing a large and varied amount of pathologic material. I am indebted to

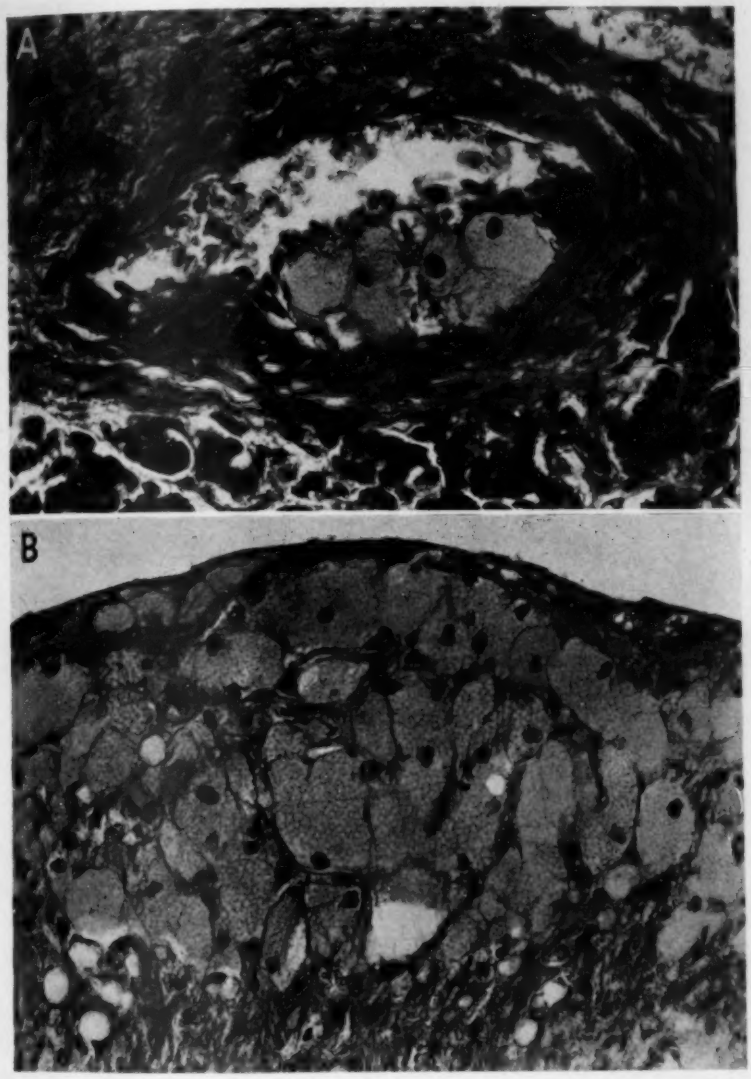

Fig. 1.—*A*, early lesion of atherosclerosis in a small pancreatic artery. × 320. *B*, section of a pinhead yellow lesion of the ascending aorta. × 350.

Dr. Frederic Parker Jr. for the example of such a lesion shown in figure 1 *A*. It is made up wholly of macrophages filled with cholesterol esters and lies beneath the endothelial layer of a small pancreatic artery.

Early stages may be found in the lesions of youth, particularly in the aorta and the coronary arteries, and even in age in the ascending portion of the aorta. These lesions tend to be temporary. They do not progress beyond the early stages because the cholesterol is removed from the

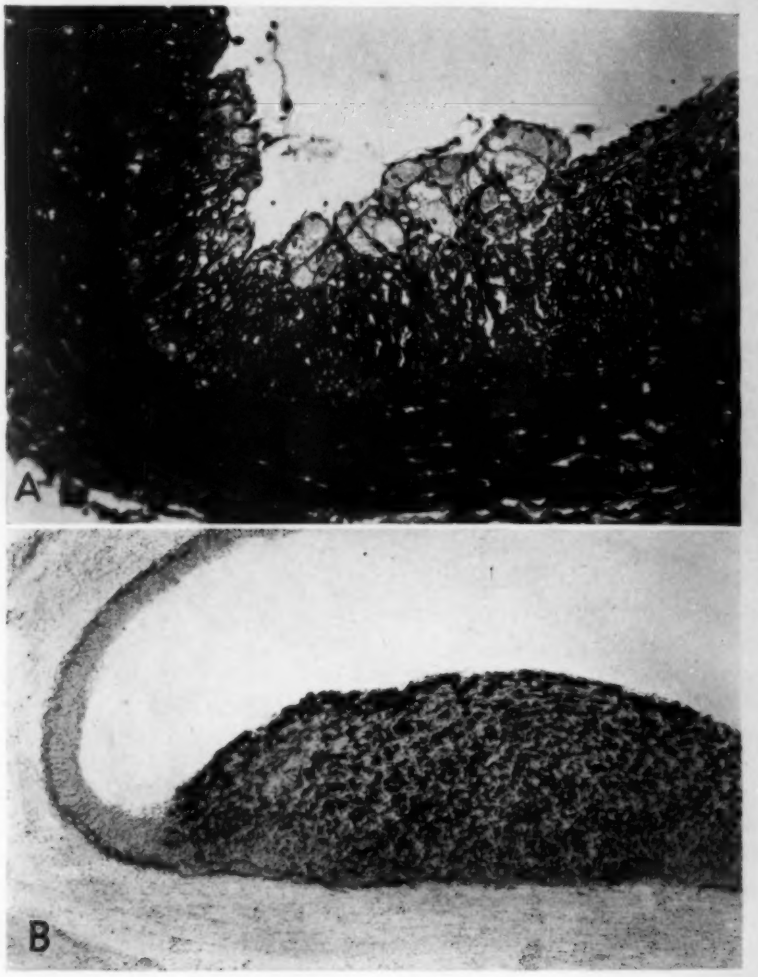

Fig. 2.—*A*, active lesion of a coronary artery in a youth of 18 years. Note the lipoid cells beneath the endothelium and the early fibrosis below. × 136. *B*, frozen section of the lesion shown in *A* but at a lower level. Sudan IV stain brings out the lipoid contained in the macrophages distributed through the young fibrous tissue. × 72.

lesions before marked secondary reactions occur. The cholesterol esters are broken down and the cholesterol is dissolved in cells which have the

appearance of fibroblasts. Following solution, the cholesterol disappears and the tissues usually return to normal. In lesions in which the process of removal has been slow, there may remain some increase of fibroblastic tissue, whose growth has been stimulated by the presence of the cholesterol. Details of this process in the arteries in youth and in the ascending aorta in age have been published elsewhere.[10] Figure 1 *B* is from a typical temporary lesion in the ascending aorta. Again the dominant figures are lipoid cells. There is no free lipoid.

Human atherosclerosis is a disease of gradual evolution, requiring years for its development to the point at which it produces clinical symptoms. From the study of advanced lesions it is evident that they repre-

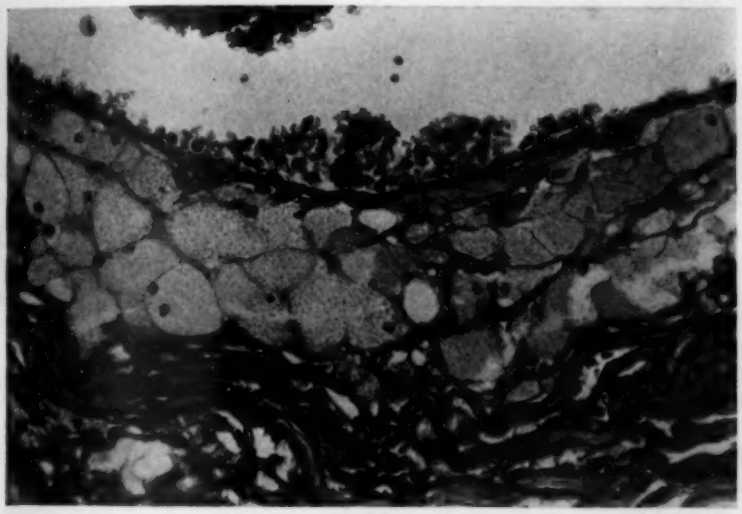

Fig. 3.—Lipoid cells underlying the endothelium and overlying collagenous bands of fibrous tissue in a coronary artery of a man of 54 years. × 280.

sent the summation of repeated deposits of cholesterol, in cells, and the reaction of the tissues to its presence. Secondary stages in this evolution arise as the irritant action of cholesterol manifests itself and cellular connective tissue is produced. Figure 2 *A* shows a group of lipoid cells lifting high the endothelial layer of the intima of the coronary artery in a lesion which is generally fibrous. Figure 2 *B* is from a frozen section of the same lesion at a point showing no new lipoid cell invasion. The fat stain (sudan IV) makes it evident that the lipoid is confined within the cells which are invading the young connective tissue of the deeper layers of the lesion. There is no free lipoid.

The intermittent character of the stages in the progression of the disease is well illustrated in figure 3. A recent collection of lipoid cells

10. Leary, T.: Arch. Path. **21**:419, 1936.

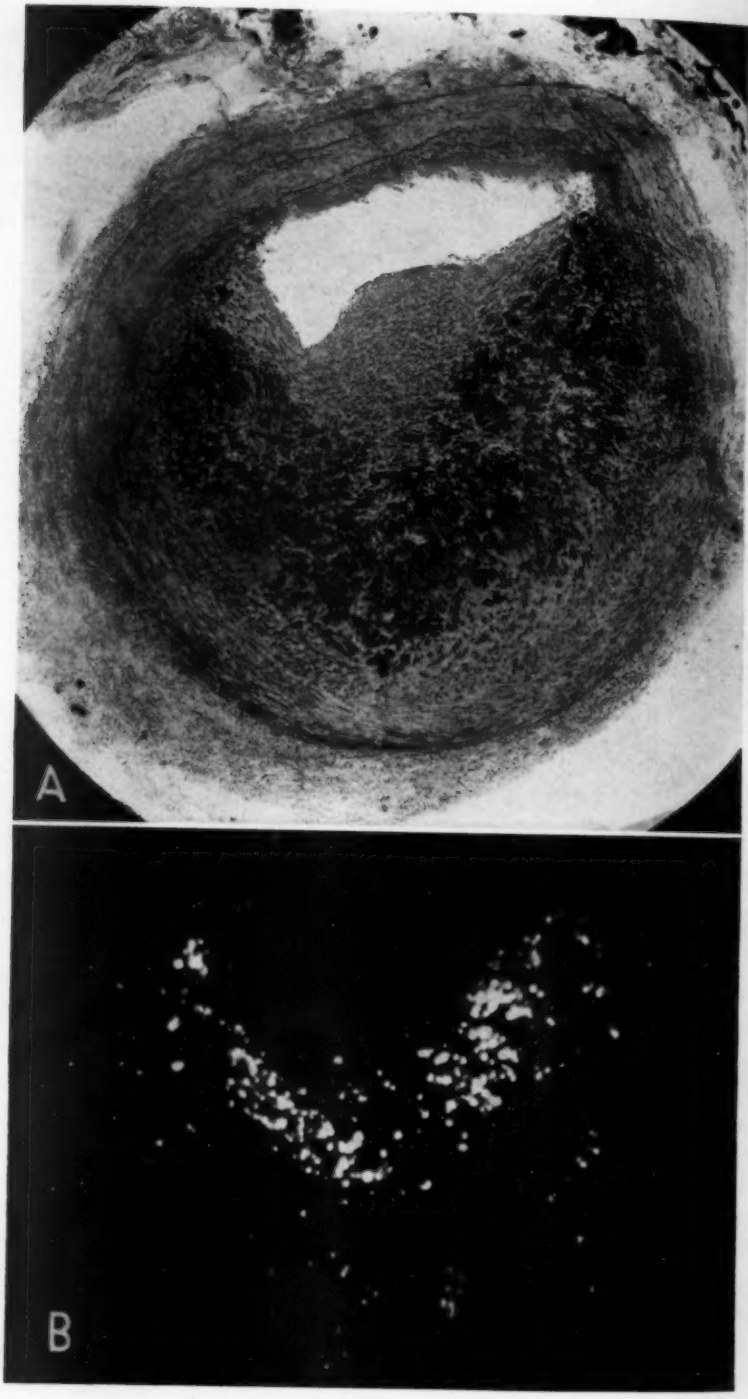

Figure 4

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underlies the endothelial layer over a dense hyaline connective tissue. The dense tissue is due to an old, scarred, quiescent process which antedated, probably by years, the recent lipoid cell reactivation of the lesion. Another sample illustrating the remittent character of the disease is seen in figure 4 *A*. A wave of lipoid cells is spreading through the deeper layers of the thickened intima, which show fibrosis. There are no longer any lipoid cells in the surface layer. Under the polariscope the anisotropic material (cholesterol esters) is evidently contained within the lipoid cells (fig. 4 *B*).

From these illustrations, which reproduce standard human lesions, it is clear that the introduction of lipoid into the subendothelial layer of the intima is primary and that the lipoid is contained within cells. These findings are supported by the results of examinations of hundreds of early human lesions. Free lipoid occurs rarely in early lesions, and its presence is manifestly due to injuries of the endothelial layer which have permitted its entrance. It is met with most commonly in older lesions, in which the necrosis and breakdown of foam cells have freed the lipoid.

If cholesterol esters are introduced into the arterial intima in foam cells, a detailed study of these cells is in order. The experimental lesions of atherosclerosis in the rabbit are particularly informative in this respect.

I. THE CHOLESTEROL LIPOID CELL: ITS GENESIS, ITS FUNCTIONS AND ITS RELATION TO THE EARLY LESIONS OF ATHEROSCLEROSIS

The cholesterol foam cell is characterized by the presence in its cytoplasm of cholesterol esters in fine droplets of strikingly equal size, so evenly distributed as to suggest a perfect emulsion. The droplets, which are anisotropic with Maltese cross markings, are separated from one another by a delicate network of cytoplasm. In fresh preparations stained for fat, the lipoid contents in isolated cells are seen to be limited within an endosarc-like internal portion, which is surrounded by a glassy ectosarc-like mantle. Among the foam cells which are found in human tissues at least 95 per cent are carrying cholesterol esters. Those bearing other lipoids (kerasin, sphyngomyelin) are relatively rare.

EXPLANATION OF FIGURE 4

A, frozen section of a branch of a human coronary artery, showing fibrosis Sudan IV stain has been taken up exclusively by the fat in macrophages invading the deeper layers of the fibrous tissue. × 50.

B, polariscopic photograph of the section shown in *A*. Apart from some lipoid dislocated in the rupture of cells by the knife, the anisotropic material is limited to lipoid cells. × 50.

In the rabbit fed cholesterol the activities of this cell can be followed under conditions which can be varied almost at will. The characteristic appearance of the cell, the anisotropic property and the reaction of its contents to fat stains, together with the distinctive coloration and texture of the cell in material fixed in Zenker's fluid and stained by Mallory's aniline blue or phosphotungstic acid methods, permit its ready identification in the tissues.

Material.—Several series of rabbits have been fed cholesterol in solution by catheter for varying periods during the last eight years. In some groups of animals the main issue was the production of high grade atherosclerosis; in others aspects of the problem dealing with the transportation and metabolism of cholesterol have been studied. In one group the animals were killed at two day intervals before and during the period of beginning deposition of cholesterol in the ascending arch of the aorta, the site of the first arterial deposit. Some animals were killed from two weeks to six months after the feeding of cholesterol was stopped in order that a study might be made of the removal of the ingested cholesterol from the liver. Some animals were fed cholesterol to the point of producing lesions, then feeding was stopped and after a long interval was renewed. Others were permitted to live up to six years after the termination of feeding. In the early work cholesterol was dissolved in sunflower seed oil for feeding purposes. In the latter period olive oil has been used as a solvent. No significant differences in the results could be attributed to the solvent used.

There is an extensive literature dealing with the experimental results of feeding cholesterol. This has been reviewed among others by Chalatow,[11] by Schönheimer,[12] by Anitschkow [6] and by Duff,[7] to whose reports the reader is referred for historical data.

THE EARLIEST LESIONS OF EXPERIMENTAL SCLEROSIS

In the rabbit there is a latent period after the commencement of cholesterol feeding before visible lesions appear in the earliest vascular site, the ascending aorta. With the ordinary dosage (0.3 Gm. per day) this latent period lasts from five to eight or more weeks after feeding begins. There is considerable variation in the reaction of individual rabbits of the same age and weight under the same dosage. In order that the initial stages of the process might be observed, rabbits 5 months old were fed by catheter 0.3 Gm. of cholesterol in olive oil daily six days a week. Animals from this group were killed at irregular intervals during the early part of the period of feeding and at two day intervals during the critical part of the period, beginning with the fourth week. The ring and the ascending aorta were cut into serial vertical strips which included the whole circumference of the vessel. After the strips were fixed in Zenker's fluid and embedded in paraffin, they were sec-

11. Chalatow, S. S.: (*a*) Die anisotrope Verfettung im Lichte der Pathologie des Stoffwechsels, Jena, Gustav Fischer, 1922; (*b*) Virchows Arch. f. path. Anat. **272**:691, 1929.

12. Schönheimer, R.: Virchows Arch. f. path. Anat. **249**:1, 1924.

tioned and stained with Mallory's aniline blue and phosphotungstic acid stains. Frozen sections were made of strips fixed in solution of formaldehyde U. S. P.

The first evidence of lipoid cells appeared in small accumulations of these cells behind the aortic cusps. Some cells were free (fig. 5 *A*); others were at most attached to the surface (fig. 5 *B*). Later, single cells or small groups of cells were found lying under the endothelial surface of the intima in the ascending aorta (fig. 6 *A* and *B*). There was no evidence of injury to the endothelium, to the underlying intima or to the media at the sites of entrance. A focus of invasion of lipoid cells having been established, new groups of these cells were added to the intial process until a lesion visible to the naked eye was produced (fig. 6 *C*). Cells could be found in the act of invading the intima (fig. 7).

Rarely, in frozen sections fat-staining material was present in the surface layer, including the endothelium, the thin underlying intima and the surface layer of the media. The fat was isotropic. This exceptional finding occurred in portions of the vessel which were not the sites of lipoid cell invasion. No evidence of anisotropic fat was found in the intima or the media until collections of lipoid cells were present. The deposit of free cholesterol esters did not usually occur until lipoid cells had broken down, freeing the esters, or until damage to the endothelial surface had arisen, usually in relation to aggregations of lipoid cells. In other words, free anisotropic fat was a rare finding.

Necrosis of the internal layers of the media was not observed until masses of lipoid cells had enlarged to the point of interfering with the diffusion of nutritive material through the intima to the medial cells most dependent on this source of nutrition, i. e., those of the internal layer underlying the intima.

The importance of these observations lies in the fact that both in man and in the experimental rabbit the initial lesion of atherosclerosis consists in an invasion of the subendothelial layer of the intima by cholesterol lipoid cells.[13] In the initial lesions, whether human or experimental, there is no swelling or disintegration of the subendothelial layer of the intima. Diffuse infiltration of the intima by free anisotropic fat is rare. There is no invasion by lymphoid cells, i. e., no inflammatory reaction. These conditions, which have been looked on as part of the primary picture, occur for the most part only after the lesions have enlarged

13. In the splenic arteries in experimental rabbits cholesterol, in solution or as free cholesterol esters, may infiltrate through the endothelial lining of the arterioles and may even lift the internal elastic lamina from its attachment to the arteriolar media. This appears to be the only exception to the rule that the initial lesion is due to the invasion of the subendothelial intima by lipoid cells. The unusual picture observed in the splenic arteries is probably due to anatomic peculiarities of these vessels.

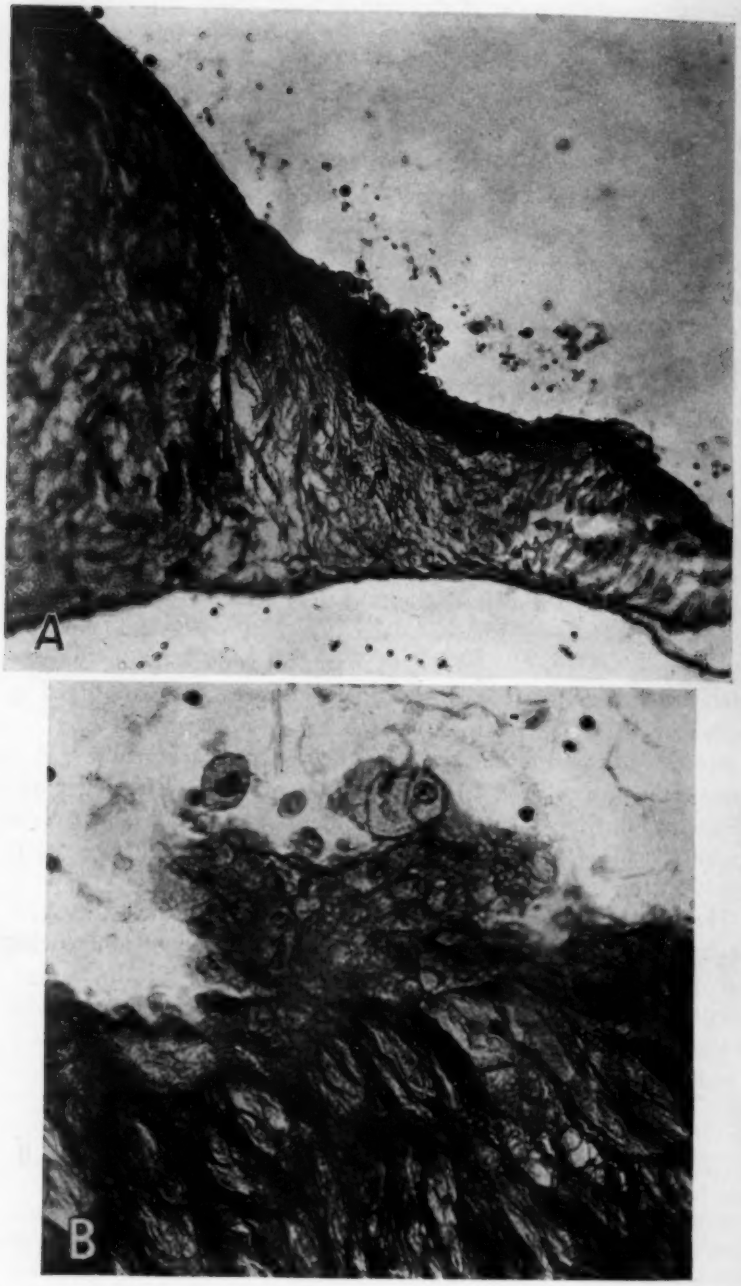

Figure 5

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beyond the initial stage. The infiltration with free cholesterol esters, when it occurs, is accidental.

Though no injury or degeneration of the vessel wall is microscopically visible at the site of the lesion, it is true that stresses play a part in favoring the lipoid cell invasion. The first localization of the

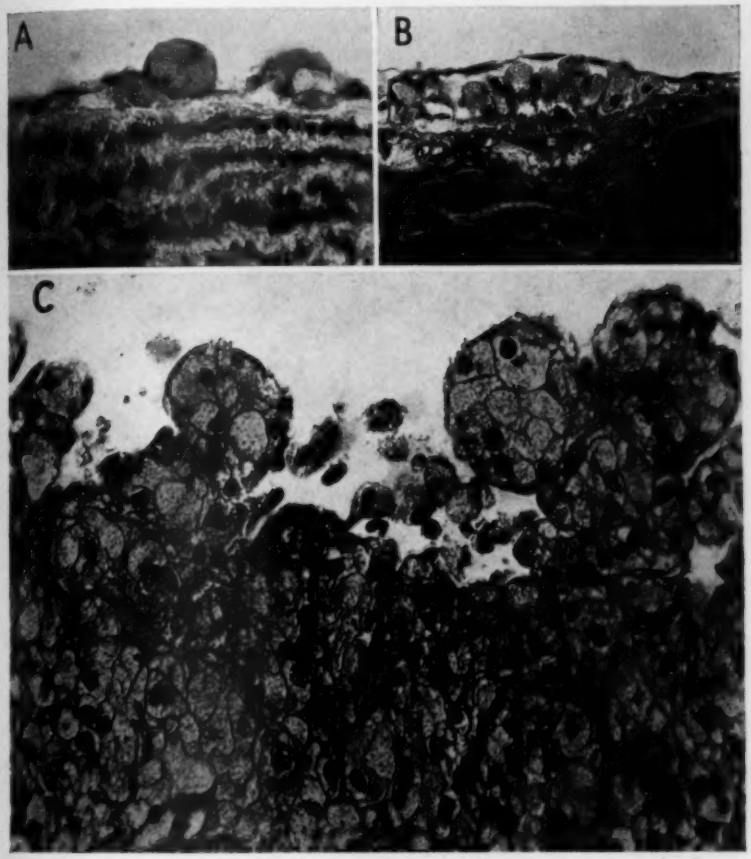

Fig. 6.—*A*, early invasion of the subendothelial layer of the ascending aorta of a rabbit. A recently attached single cell is seen. × 417. *B*, lipoid cells beneath the endothelium with thickening of the subendothelial layer of a rabbit blood vessel. × 261. *C*, massed lipoid cells in an early lesion in a rabbit. Note the invading cell on the surface at the center. × 409.

Explanation of Figure 5

A, section of an aortic cusp of a rabbit. Free and attached lipoid cells may be seen in the clump in the center. Note the relatively acellular character of the tissue of the cusp. × 142.

B, collection of cells, free and attached to the musculofibrous wall of a rabbit sinus of Valsalva. × 460.

lesions in the ascending aorta probably has a relation to conditions of stress in this region. With the closure of the aortic cusps the ascending aorta is subjected momentarily to greater stress than any other part of the arterial system. The pressure is then generalized and reduced by the elastic aorta. This stress, to which the proximal portions of the coronary arteries are also subjected, probably accounts for the apparently selective frequency of coronary sclerosis, though the systolic pressure to which these vessels are exposed while their muscular branches are compressed is also an important factor.

It is also undoubtedly true that foci of injury to or modification of the intimal tissues, as in syphilis, favor the entrance of lipoid cells.

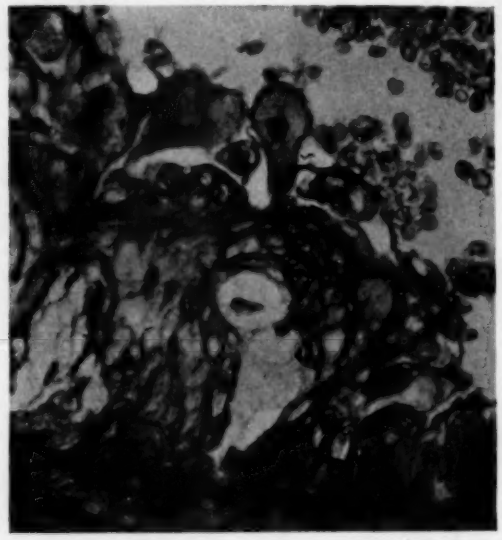

Fig. 7.—Lipoid cells invading the intima of a rabbit's innominate artery. × 500.

THE SOURCE OF THE CHOLESTEROL ESTERS

It is generally accepted that cholesterol is esterified in the adrenals, in which the substance is stored in this form. Chalatow [11] recorded the presence of isotropic fat drops in the adrenal of the experimental rabbit and the conversion of the cholesterol content of these drops into anisotropic esters, apparently by cells of the adrenal cortex.

It has been assumed that the liver also esterifies cholesterol. This assumption is based on the observation of Thannhauser and Schaber,[14] since confirmed by others, that in "parenchymatous" disease of the liver there is a lowering of the ratio of ester to total blood cholesterol. The study of livers of experimental rabbits killed during the latent period is illuminating in this respect.

14. Thannhauser, S. J., and Schaber, H.: Klin. Wchnschr. **5**:252, 1926.

In frozen sections the material first showing evidence of deep staining with sudan was the blood, causing the sinusoids to stand out from the background of liver cells. It is curious that polariscopic evidence of cholesterol esters in blood plasma is not obtainable, however rich the blood may be in esters. As feeding progressed, sudan-staining material collected in some concentration along the borders of the sinusoids (fig. 8*A*). Studies of frozen and paraffin sections disclosed that the fat was contained not only in the sinusoids but particularly in the lymph spaces between the Kupffer cells and the liver cells. The fat was isotropic, i. e., it was neutral fat, but undoubtedly it carried cholesterol in solution. Then isotropic fat appeared in the liver cells in small amounts. The first anisotropic fat arose in liver cells in the central portions of the lobules in the form of cholesterol esters. It can be asserted, therefore, on direct evidence that cholesterol is esterified in the liver.

It has been recognized since the early studies of experimental atherosclerosis that the Kupffer cells are active in the liver of a rabbit under cholesterol feeding. Since the usual function of these cells consists in the removal of particulate matter from the blood stream it was thought that these cells removed cholesterol esters from the blood stream and transferred the material to liver cells. Examination of sections of livers during the latent period revealed no evidence of any activity on the part of the Kupffer cells until the latter part of the period, at which time considerable collections of cholesterol esters had accumulated in the liver cells of the central portions of the lobules. It can therefore be asserted further that esterification of cholesterol appears to arise from the functioning of the liver cell and not from that of the Kupffer cell.

Studies of human fatty livers and of livers from experimental rabbits indicate that fat which has undergone desaturation in the liver is set free into the sinusoids or central veins directly. Cholesterol esters in normal amounts appear to be delivered in a similar manner from the liver cells to the circulating blood, without the intervention of other cells.

As cholesterol esters accumulate *in excess* in the liver cells of the experimental rabbit, however, the functioning of a new factor, the Kupffer cell, requires attention. As feedings progress Kupffer cells swollen with ester burdens become more and more abundant in the sinusoids. The activities of these and similar cells furnish a clue to the probable source of the lipoid cells producing atherosclerosis.

THE SOURCE OF THE LIPOID CELLS

Anitschkow [6] discussed the probable source of the lipoid cells in atherosclerotic lesions as follows:

> The question of where the lipoid cells just described come from is difficult to decide. Various views have been advanced by Anitschkow (1913), Saltykow

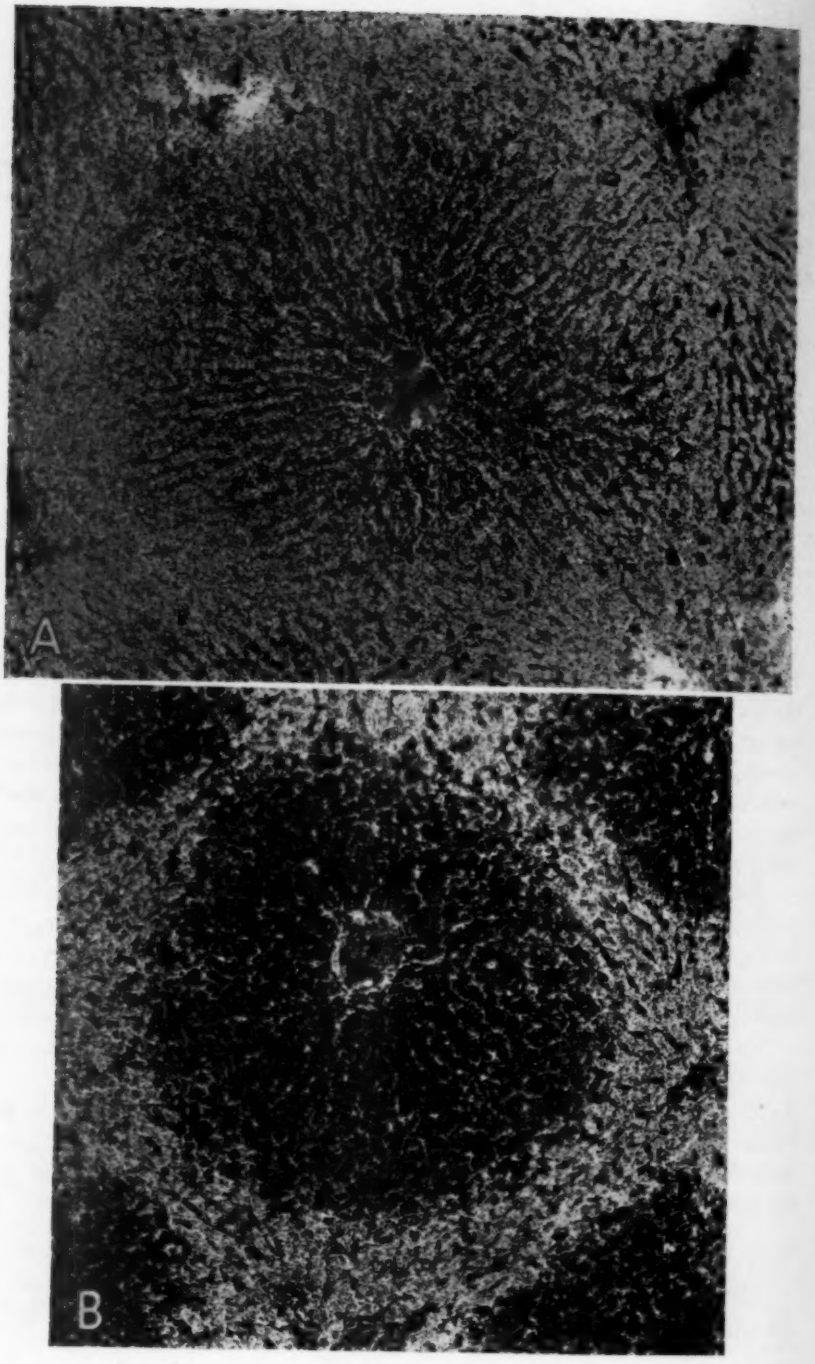

Figure 8

(See legend on opposite page)

(1913b), and Versé (1925). These cells might originate either from the endothelial cells of the artery concerned or from the connective tissue cells of the inner layers of the arterial wall or from wandering lymphoid or monocytic cells. My own investigations have led me to conclude that endothelial cells cannot be involved, because throughout the entire process in all its stages they form a simple and single layer of flat cells overlying the surface of the changed parts, and they do not contain any lipoid globules. No transitional forms are to be found between them and the lipoid phagocytes. Nor is it likely that the connective tissue cells might be found between the latter and the endothelium. For in rabbits the endothelial cells directly adjoin the internal elastic lamella. Granting even that some isolated connective tissue cells might be found between the latter and the endothelium, this would be of no significance, unless they exhibited a considerable numerical increase and transformation into lipoid cells, with the latter accumulating in great numbers in the newly formed intima. But no such process has ever been observed. On the contrary, one can see quite distinctly all conceivable transitional forms between the small lymphocytic and monocytic cells on the one hand, and the large lipoid cells on the other, so that development of the lipoid cells from the free mononuclear cells, probably derived from the blood, would seem to be the most plausible hypothesis of their origin. This is also suggested by the fact that lymphoid or monocytic cells frequently seem to invade the aortic wall directly from the lumen.

Duff [7] considered three possible sources of these cells: (*a*) The foam cells could have migrated from the media, which source he excluded. (*b*) "There are those who believe that the macrophages enter the intima from the lumen of the artery." (*c*) The cells could arise from a multiplication of wandering mononuclear phagocytes present in the intima prior to the appearance of lipoids.

ORIGIN OF LIPOID CELLS FROM THE LIVER?

As cholesterol feeding is continued through the latent period cholesterol esters accumulate in such amounts that all of the liver cells except the most peripheral group become crowded with the lipoid (fig. 8*B*). The mass of lipoid becomes so great that extraordinary procedures have to be adopted for the removal of the excess. If rabbits which had received very large doses of cholesterol were permitted to live for weeks or months after feeding was stopped, a hitherto unrecorded reaction was found to have occurred in their livers and adrenals. For example, in some livers there were seen series of brownish deposits beneath the capsules at nodal points. Frozen sections disclosed masses

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EXPLANATION OF FIGURE 8

A, frozen section of a liver lobule of a rabbit, stained with sudan IV. The trabeculae are outlined by stained lipoid. The liver cells are largely free of fat. × 80.

B, frozen section of a liver lobule of a rabbit, stained with sudan IV. The liver cells are filled with lipoid (cholesterol esters). × 80.

of fat-staining material within vessels, apparently lymphatics (fig. 9 *A*). In other sections the sublobular lymphatics throughout the organ were filled with similar material (fig. 9 *B*). In paraffin sections the lymphatics were seen to be crowded with foam cells (fig. 10 *A*), and in the central portions of the lobules were numbers of single cells in intercellular spaces. The lipoid cells first appeared in the sinusoids and the trabeculae and accumulated in lymph spaces in the central portions of the lobules. The lymph vessels first filled were those in the proximal portions of the lobules about the central veins; next in order came those about the sublobular veins, and finally those about the portal veins and beneath the capsule of Glisson. From the number of lymph vessels which were seen in advanced processes it is probable that new lymph vessels are formed as the cells increase and obstructions are produced.

The Lipoid Cells in the Hepatic Lymphatics.—In paraffin sections stained with Mallory's phosphotungstic acid stain it became clear that the cells which crowded the lymphatics were Kupffer cells (fig. 10 *B*). Every stage could be followed within the lobules from the progressive filling of these cells with cholesterol esters as they lay in the sinusoids to their ultimate delivery into the lymphatics. Figure 11 *A* shows a Kupffer cell lying along the wall of a sinusoid and partially filled with esters, probably extracted from neighboring liver cells. In figure 11 *B* three Kupffer cells containing lipoid lie in a sinusoid. In figure 11 *C* a filled lipoid cell lies on or in a liver trabecula. In figure 11 *D* a lipoid cell is embedded in a fatty liver cell in a trabecula. Figure 11 *E* shows a large lipoid-filled cell entering a lymph space or vessel alongside the central vein. In most of these illustrations cells other than those referred to are seen in sinusoids or lymph spaces. In places agminated masses of lipoid cells were found.

The Lipoid Cells in the Hepatic Blood Vessels.—In addition to the cells which crowded lymphatics, lipoid cells occurred in numbers in the hepatic veins. Figure 12 *A* shows a group of cells being extruded from a sinusoid into a vein. The central portions of the liver lobules in advanced processes contain large numbers of lipoid cells in lymph spaces, and there is a relative increase in connective tissue, probably due to cholesterol stimulation, as is seen in this photomicrograph. This disorganization of the central portions of liver lobules must interfere with the normal sinusoidal circulation. The projecting edge of the sinusoid opening through which cells are being delivered in figure 12 *A* conforms to the modern concept of a valvelike action at the ends of the sinusoids. Figure 12 *B* illustrates free lipoid cells in a hepatic vein. Probably because of the relatively rapid movement of the blood and the size of the veins, obstruction of blood vessels other than the sinusoids does not occur.

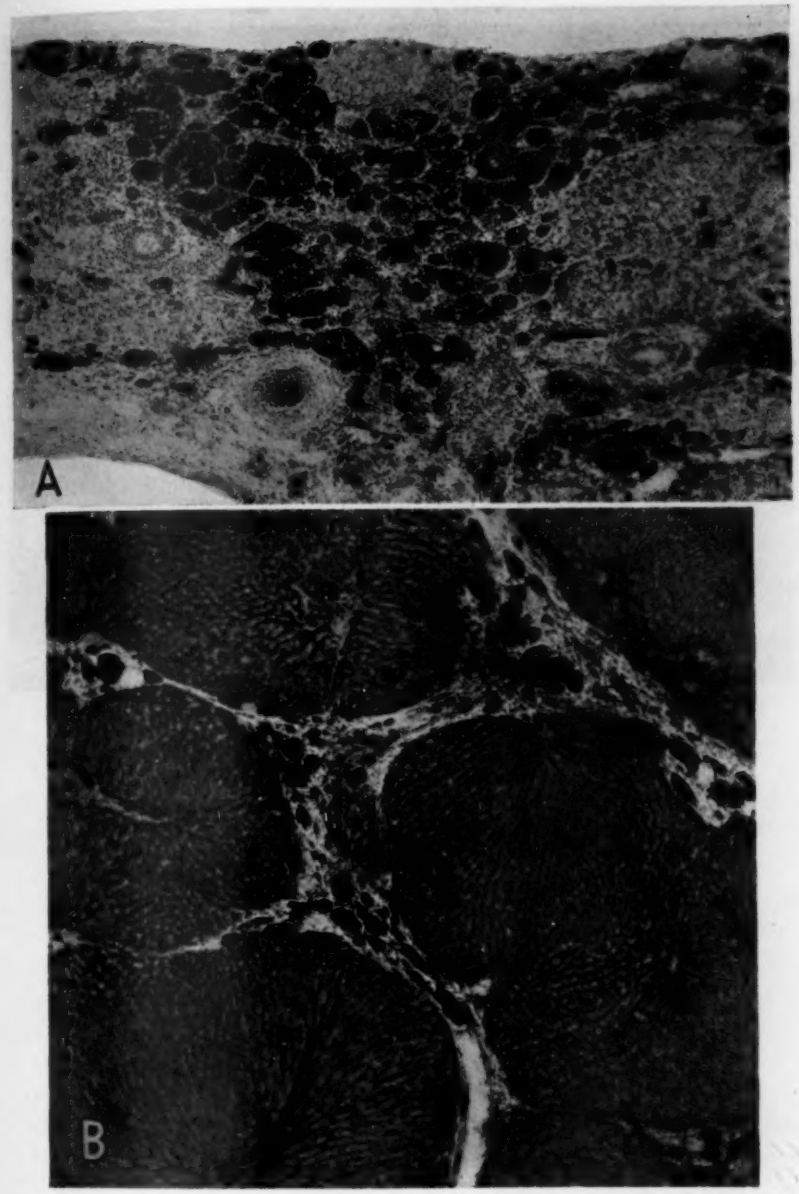

Fig. 9.—*A*, frozen section of rabbit liver, stained with sudan IV. The subcapsular lymphatics are filled with lipoid. × 68. *B*, frozen section of rabbit liver, stained with sudan IV. The lymphatics are filled with lipoid. × 56.

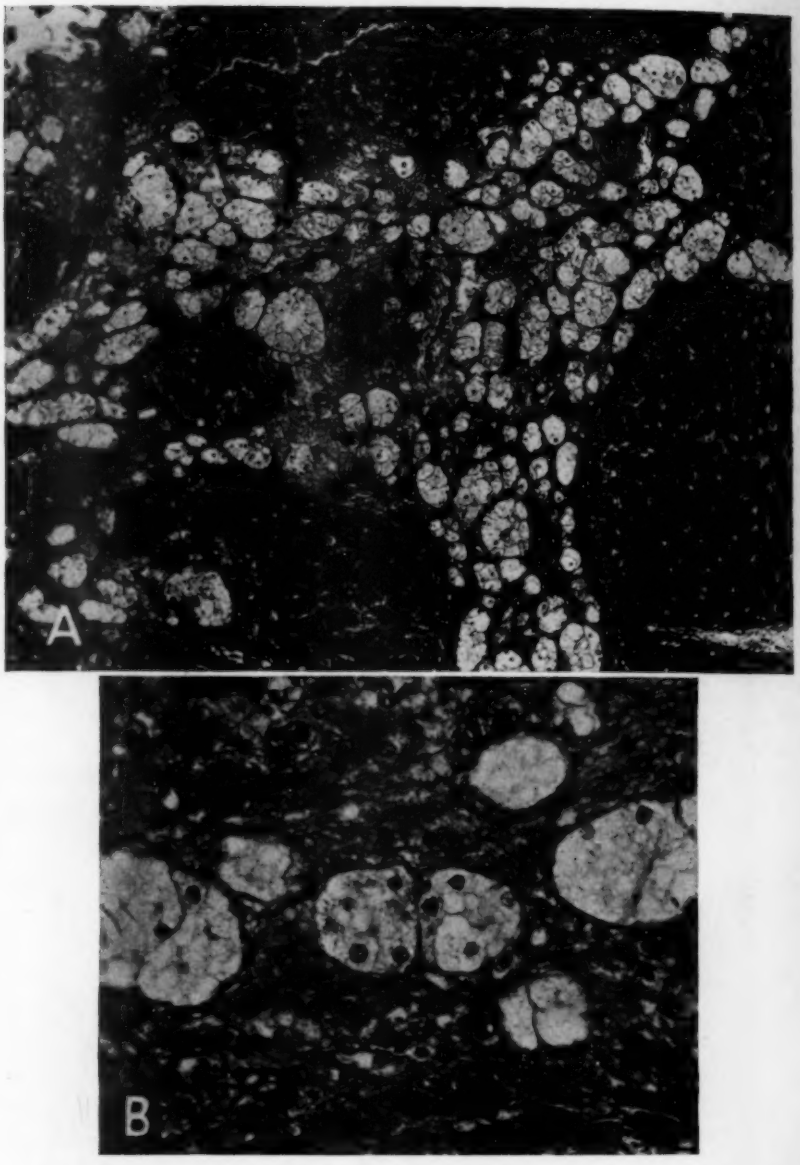

Fig. 10.—*A*, paraffin section of rabbit liver, stained with Mallory's phosphotungstic acid. Lipoid cells are crowding the lymphatics. × 94.5. *B*, detail of *A* at higher magnification. × 340.

ORIGIN OF THESE CELLS FROM THE ADRENALS?

Step by step, as lipoid cells accumulated in the liver, so they came to crowd the adrenal lymphatics. The cells lining the sinusoids of the

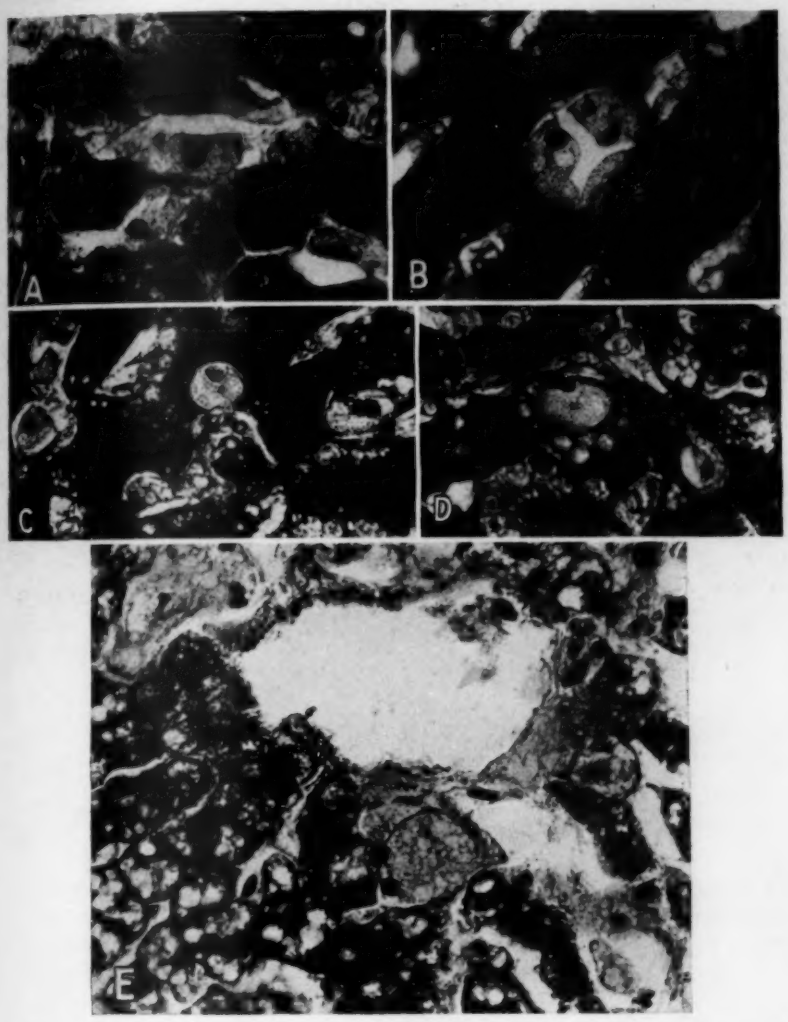

Fig. 11.—*A*, Kupffer cell partly filled with lipoid in a sinusoid. × 589.5 *B*, three or more lipoid cells in a sinusoid. × 589.5. *C*, lipoid cell in or on a trabecula. × 443.5. *D*, lipoid cell surrounded by a fatty liver cell. × 443.5. *E*, lipoid cell invading a lymph space about wall of the central vein of a lobule × 460.

adrenal glands correspond to Kupffer cells in their relation to the vessel walls and are looked on as comparable cells of the reticuloendothelial

system. In cholesterol-fed animals the adrenal glands undergo marked enlargement, to several times the normal size (fig. 13 *A*). This enlargement is dependent on the increase in the cholesterol intake. Normally the adrenals are the only glands which contain relatively gross masses

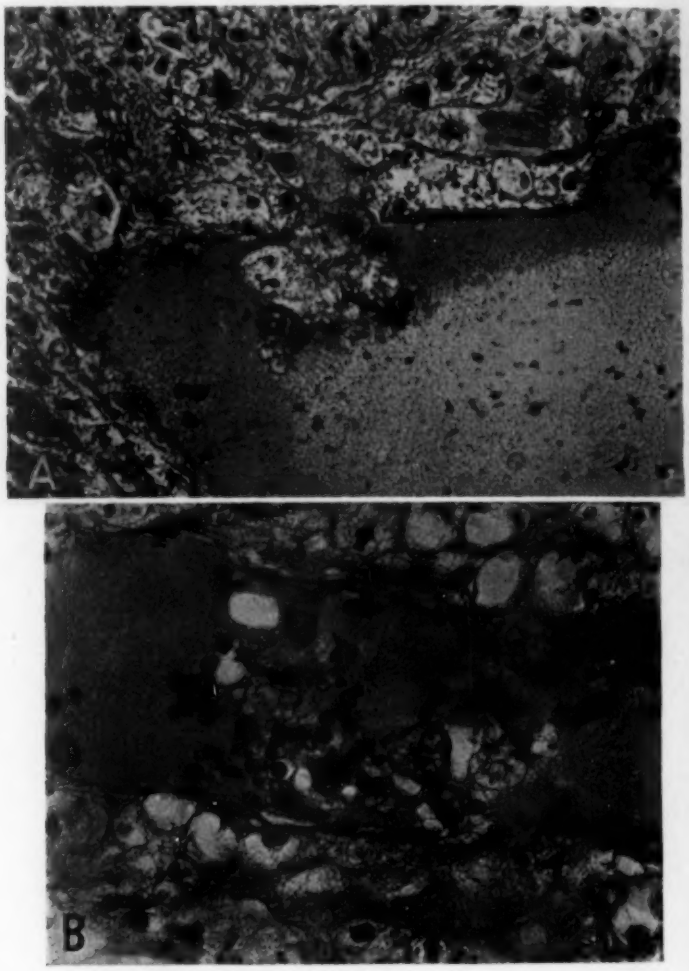

Fig. 12.—*A*, lipoid cells being extruded into the central vein of a lobule. × 400. *B*, lipoid cells in a vein of the liver. × 400.

of cholesterol esters. Normally the cells of the glomerular zone contain little ester cholesterol. The cells of the fasciculate zone are rich in lipoids, principally cholesterol esters, while the cells of the reticular zone contain less. In the enlarged glands under cholesterol feeding cells of all zones may be rich in cholesterol esters.

After massive feeding of cholesterol the lymph vessels of the medulla, difficult to demonstrate in the normal adrenal, may be enormously dilated with lipoid cells and come to occupy much more space than the normal medullary tissue (fig. 13 *B*). Under staining with Mallory's phosphotungstic acid–hematoxylin these cells take a faint blue stain and are differentiated by their color and texture from the normal cortical cells. They can be found in the cortex, including the glomerular zone (fig. 14 *A*), and apparently make their way through the tissues to the

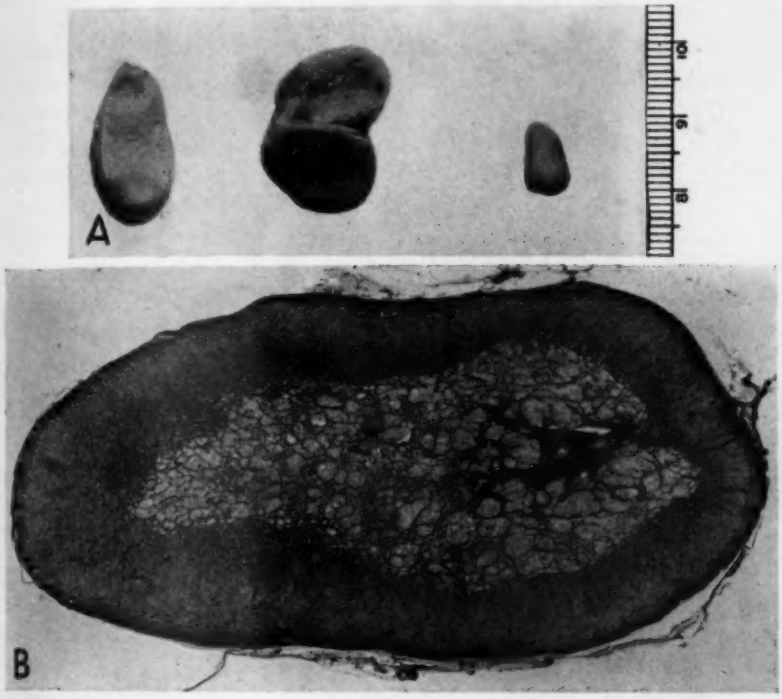

Fig. 13.—*A*, gross photograph of rabbit adrenal glands. Comparison of a gland of normal size with glands from cholesterol-fed rabbits. The enlarged glands have been incised for fixation. The normal gland for comparison is at the right. *B*, section of an enlarged adrenal gland showing dilated lymphatics filled with lipoid cells. × 8.5.

medullary lymph vessels, which they obstruct (fig. 14 *B*). The lipoid cells which distend and block the lymph vessels commonly show degenerative changes. Disorganization, rupture and fusing of the cells are met with, and occasionally a foreign body giant cell is produced. These degenerative changes are much more definite in the cells in the adrenal lymphatics than in those in the lymphatics of the liver.

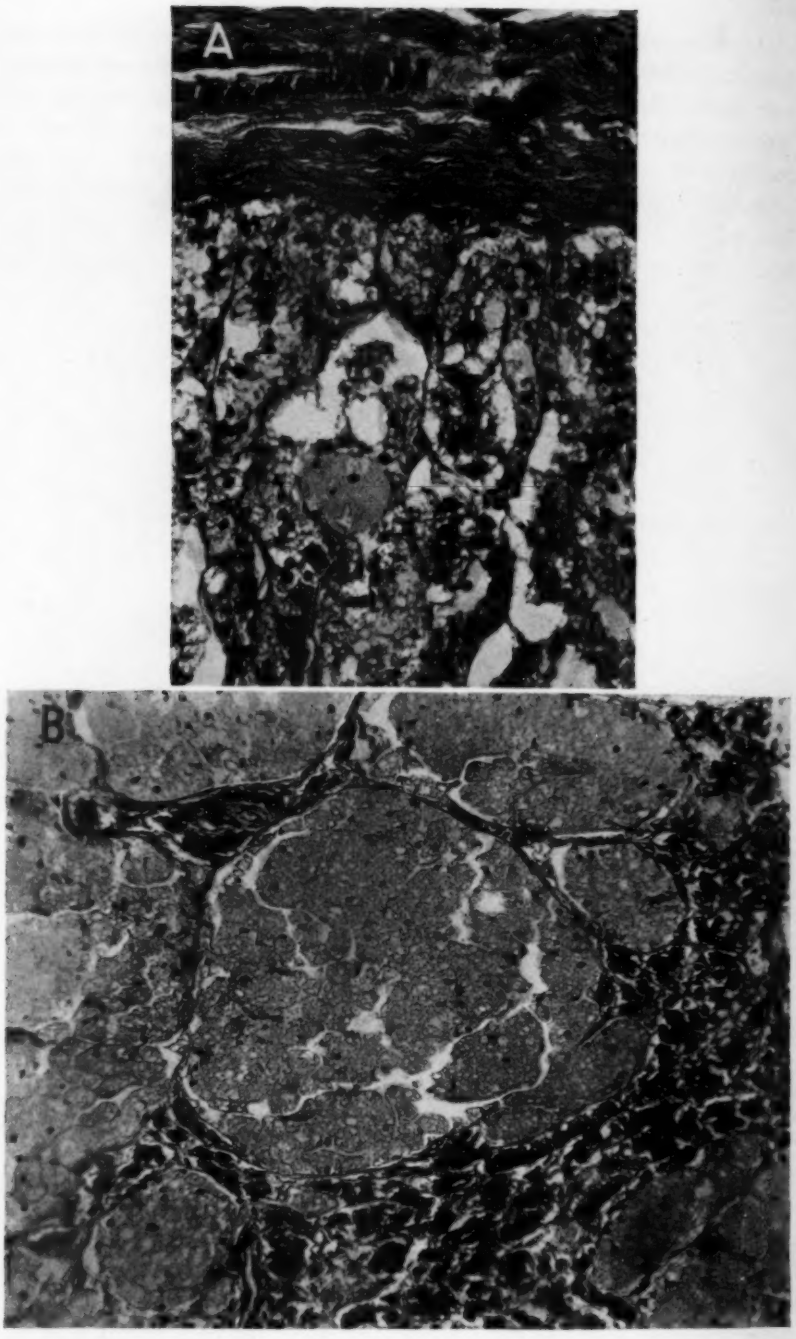

Fig. 14.—*A*, adrenal cortex near capsule. Lipoid cells may be seen. × 250. *B*, dilated lymphatics in an adrenal. The medulla is filled with lipoid cells, which are fused, many undergoing disorganization. × 141.5.

The overcrowding of the lymphatics with lipoid cells can represent only a complete breakdown even of the emergency procedure adopted for the removal of the excess cholesterol esters from the liver and the adrenals. In efforts to produce in experimental animals in months a disease process which in man requires years for its evolution dosages were used that are overwhelming for the weak cholesterol metabolic system in the rabbit. The very excess of the reaction, however, has served three purposes: First it slowed up the activities of the phagocytic cells, whose peregrinations through the liver and adrenal tissues could then be followed in detail; ordinarily the Kupffer cell loaded with cholesterol esters has but to loosen its hold on the sinusoidal wall and it is swept into the circulation and out of the liver. Second, it served to illustrate on a grand scale the productivity of cells of the Kupffer type under extreme stimulation. Third, through the obstruction it produced a natural injection of the lymphatics of the organs, thus clearing up their topography.

The significance of the latent period following the beginning of cholesterol feeding becomes manifest from these studies. The delay before lipoid cells appear in the aorta is necessitated for two reasons: 1. Cholesterol esters must be produced *in excess* by the functioning of the hepatic and adrenal cells. 2. Phagocytic cells capable of removing the excess esters must be formed, set free and carried to the sites of deposit.

THE PASSAGE OF LIPOID CELLS THROUGH THE LUNGS AND INTO THE ARTERIAL INTIMA

Lipoid cells which have escaped from the liver and the adrenals are brought to the lungs as passive agents in the blood, but the journey through the lungs again demands ameboid activity of the cells. Examinations of lung sections from animals killed during the latent period showed no lipoid cells, as one would expect. Examinations of lung sections from many of the animals killed after this period were also without results. The lung sections from other animals in this group, however, were rich in collections of such cells in the pulmonary veins. The cells tended to congregate in masses (fig. 15 *A*). They were even more abundant in venules, some of which they filled (fig. 15 *B*). The cells were in general smaller than those seen in the liver and adrenals and conformed in a marked degree to a standard size. They were more compact, and the cell bodies stained more deeply.

In the passage of the capillaries in the lungs the lipoid cell bodies, identifiable by their texture, were elongated and distorted as they accommodated themselves to the sinuous curves of the alveolar capillaries. The nucleus was usually at one end of the cell and at a focal plane different from that of the body of the cell (fig. 16 *A*). In dilated regions in the

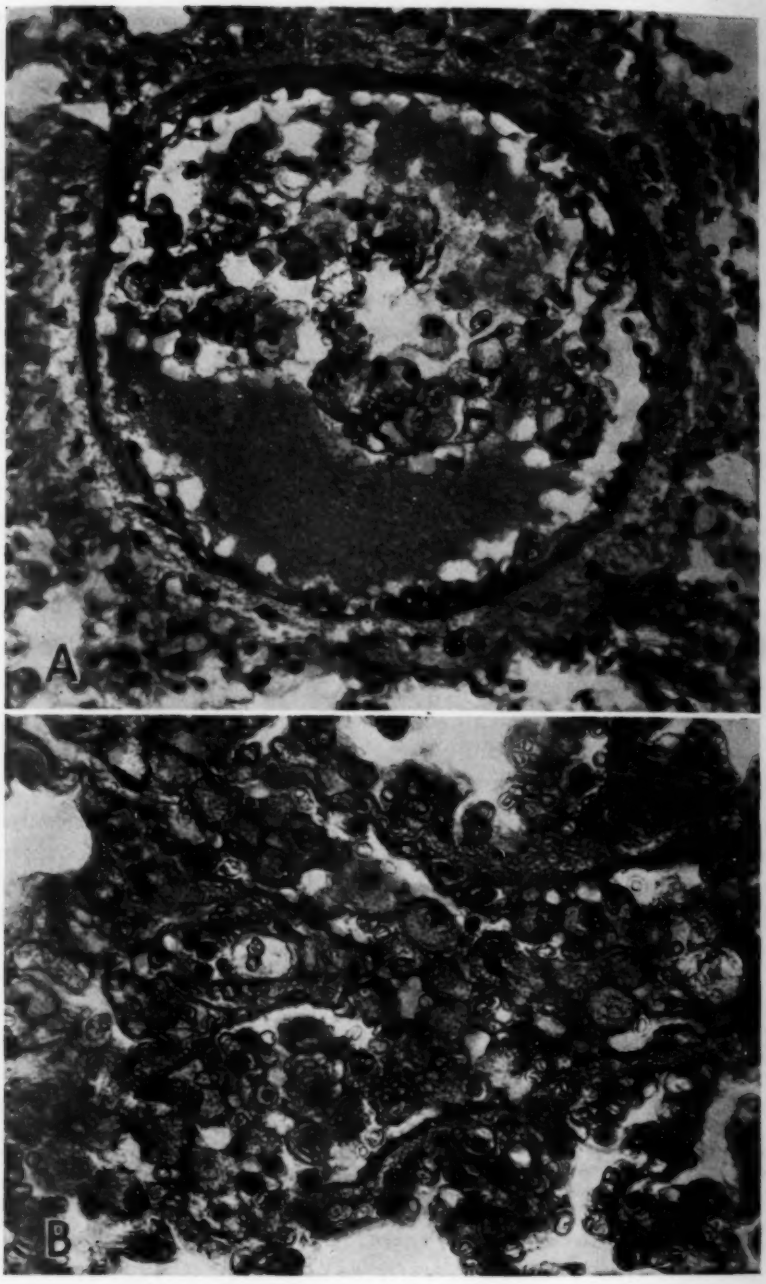

Fig. 15.—*A*, branch of a pulmonary vein containing lipophages in coherent masses. × 360. *B*, junction point of two pulmonary venules occupied by lipophages. × 460.

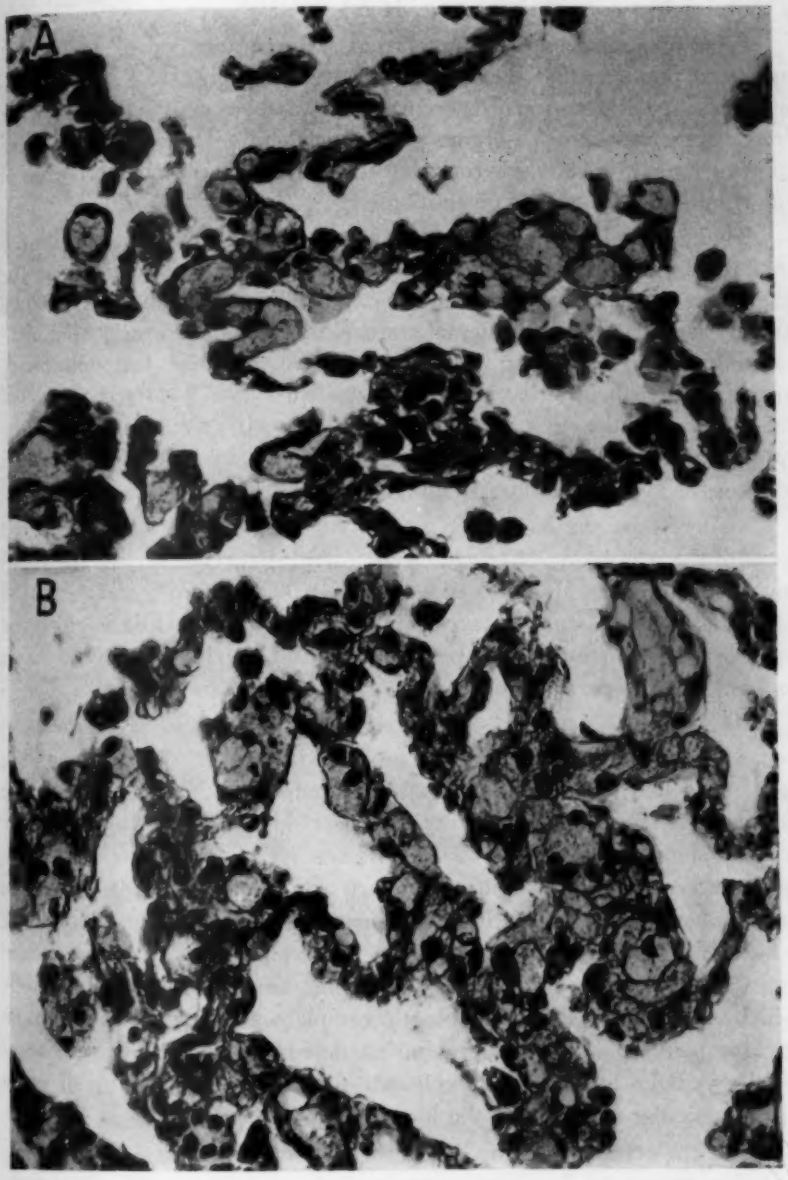

Fig. 16.—*A*, lipophages passing through capillaries of alveolar walls. Note the distortion of one cell to the left as it is passing through a sharp kink in a capillary. × 460. *B*, large collection of lipophages passing through lung capillaries—apparently in a region where obstruction has occurred. × 434.5.

capillaries and the finer venules the cells were able to expand and assume a more or less normal shape (fig. 16 *B*).

From examinations of lungs from a large number of animals it appeared probable that the passage through the lungs, at least as far as mass passage was concerned, occurred in waves of cells which were set free at intervals from the organs producing them. The cells in the veins in some lungs were so numerous that they could not reasonably represent the results of passage at a given moment.

Kiyono [15] in his study of vital-staining with carmine satisfied himself that the large cells of the type of megakaryocytes are retained in the capillaries of the lungs and that the large cellular elements of the blood are filtered off. In experimental animals the pulmonary veins contained more histiocytes carrying carmine particles than did the pulmonary artery. He believed that this effect was produced by the collapse of the lungs when the chest was opened. The blood in the capillaries of the lungs was thus forced out into the pulmonary veins with the red cells, leaving the capillaries almost empty.

Evidently on the basis of Kiyono's work, Aschoff [16] has stated that most of the wandering phagocytic cells carrying foreign bodies are sifted out in the lungs. Many of those which pass the lungs are destroyed in the left ventricle. "But a certain number of the reticulo-endothelial cells or blood histiocytes do pass the filter of the lungs and the heart and enter the general circulation."

My own studies of the lung traverse by lipophages are impressive because of the amazing number of cells which were observed passing what is looked on as a filter capable of removing these cells from the circulation. These cells, however, are ameboid and normally make their way through the interstices of solid tissues. Passage through the relatively large pulmonary capillaries, which are capable of ready distention on the alveolar side and lie in a loose-textured thin membrane, should be relatively easy. From the appearances in the pulmonary capillary system and the venules it is probable that not some but most of the lipoid cells which reach the lungs are able to complete the transit. The most striking pictures of cells undergoing passage are found in the peripheral portions of the lungs, though cells are found in capillaries in all parts of the vesicular structure of the lung.

That the crowding of capillaries with lipoid cells is probably responsible for stresses in the pulmonary circulation is a reasonable deduction. These stresses in turn are probably accountable for invasion of the

15. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

16. Aschoff, L.: Lectures in Pathology, New York, Paul B. Hoeber, 1924 p. 17.

pulmonary intima, reproducing early human lesions (fig. 17). Apart from lesions of the pulmonary arteries it was remarkable how free of fat-staining material the lungs could be. In some cases interstitial groups of cells had invaded the interlobular tissue, for the most part near the pleura. Even in lungs showing massive transit of cells through the capillaries, few cells had escaped into the alveoli. Though the capillaries were dilated and were bulging at points where lipoid cells were passing, rupture into the alveoli occurred rarely. The production of lipoid pneumonia by the accidental intratracheal escape of cholesterol in oil is a thing apart and will be dealt with in part II.

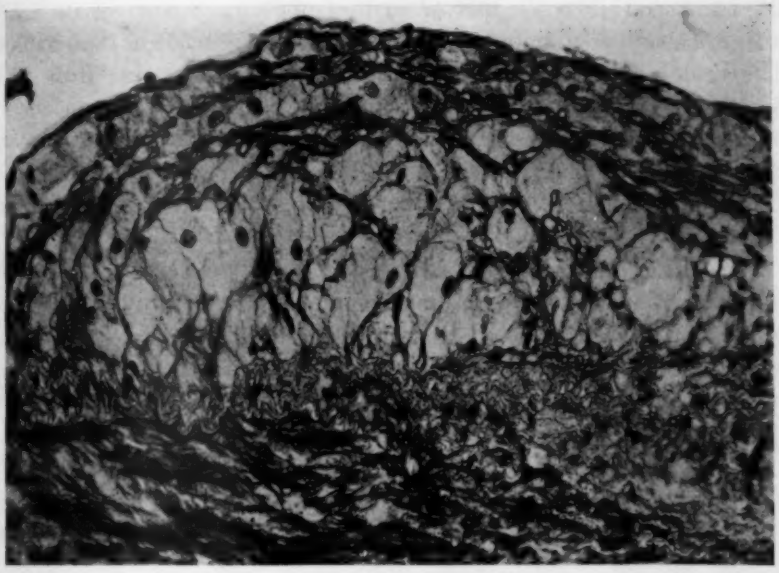

Fig. 17.—Massed lipophages in the intima of a rabbit's pulmonary artery. Compare with the similar human lesion in figure 1 *B*. × 290.

The shrinkage in size of the lipoid cells in their passage through the lungs and their more compact structure as seen in the pulmonary veins imply a probable loss of part of their cholesterol content. The cells in the sinuses of Valsalva and the newly arrived cells in the lesions in the ascending aorta show similar permutations. It is difficult to account for these changes on mechanical grounds alone. Studies of the effect of passage through the lungs on the cholesterol content of the blood offer a possible clue to the cause of this peculiar effect. Abelous and Soula [17] recorded that the blood from the right side of the heart in the dog con-

17. Abelous, J. E., and Soula, L. C.: Compt. rend. Soc. de biol. **85**:6, 1921.

tained on the average 259 mg. more cholesterol per liter than the blood from the left side. The process appeared to be one of cholesterolysis. Bouisset and Soula [18] demonstrated that the cholesterolysis in the lungs was dependent on ventilation. During asphyxia there was an increase in cholesterol in the systemic blood, counterbalancing the difference in content between the blood in the left and in the right side of the heart. Rapid respiration induced by heat, on the other hand, increased the difference between the blood content from these sources. That cholesterol-bearing cells should also lose part of their contents in the lung transit is a not unreasonable inference.

As lipoid cells come to rest in the interstices of tissues, whether in the lesions of atherosclerosis or in the subpleural tissues of the lung, it is probable that additions to the ester content are made as time elapses. The cells may become very large, their bodies distended with ester droplets. This capacity for achieving great size and the "stickiness" of the cells, which causes them to cohere in masses, are the outstanding characteristics of Kupffer cells, as studied in pure culture by Beard and Rous.[19] Histiocytes, on the other hand, are smaller cells, are less "sticky" and take up smaller amounts of foreign bodies.

In this connection it should be noted that cholesterol foam cells tend to continue to bear their lipoid contents up to the death and disintegration of the cell. This is in contrast to the accepted belief that the histiocytes or microgliocytes observed in the region of brain and other hemorrhages carry their burdens of blood pigment to blood vessels, deliver themselves of their contents and return for a fresh supply.

Localization of Lipoid Cells in the Arterial Wall.—In the early stages of experimental atherosclerosis the invasion of the intima by lipoid cells filled with cholesterol esters is highly selective and limited to the arteries. Furthermore, with small doses that more closely approximate the probable doses producing the human disease, the invasion tends to be arterial almost exclusively, even to the end of the experiment. Massive or long-continued dosage results in delayed wide distribution of the lipoid cells in various tissues of the body.

The peculiar affinity of the cholesterol lipoid cells for arteries is probably due to chemotaxis. This chemotaxis must be related to the cholesterol content of the cell, since macrophages carrying other forms of particulate matter do not invade the subendothelial layer of the intima. Macrophages in man and in experimental animals in which a great variety of forms of particulate matter have been engulfed, including silica and silicates, carbon, magnesium dioxide, lapis lazuli, mercuric

18. Bouisset, L., and Soula, L. C.: Compt. rend. Soc. de biol. **99**:1206, 1928.
19. Beard, J. W., and Rous, P.: J. Exper. Med. **59**:593, 1931.

sulfide, colloidal dyes, bacteria, blood pigment and other agents, exhibit no tendency to invade the arterial walls.

An exception to this rule has been recorded recently. According to Hueper,[20] intravenous and intraperitoneal injections of solutions of polyvinyl alcohol in dogs gave rise to lesions of the aorta and arteries resembling those of atherosclerosis. Macrophages carrying the material were found in the subendothelial layer of the aorta, and Kupffer cells in the liver had multiplied and engulfed the substance as colloidal particles. Polyvinyl alcohol, used industrially as a plastic because of its apparent inertness, occurs as a white powder. It can be dissolved in physiologic solution of sodium chloride to form a colloidal solution. That the substance is not inert is evident from the reports of Hueper, Landsberg and Eskridge[21] who observed in dogs a progressive, usually fatal, anemia with leukocytosis following its use. Polyvinyl alcohol does not occur naturally in the human body. It is not a usual or necessary part of the diet. It will produce vascular lesions when injected intravenously. It is not closely allied to the fats and does not tend to form esters with fatty acids. No considerable latent period before experimental lesions appear has been recorded. The macrophages apparently engulf the alcohol directly as a colloidal substance without further modification.

Cholesterol, on the other hand, does occur naturally in the body, is a usual and apparently necessary part of the diet, will not produce atherosclerotic lesions after intravenous injection, is closely allied to the fats and does form esters with fatty acids; it appears in macrophages in the arterial intima only after a long latent period, following esterification of the substance in excess. The relation of lesions due to polyvinyl alcohol to those of human and experimental atherosclerosis is, therefore, largely academic. The substance, however, does provoke a reaction with phagocytic activity and affinity for the arterial intima resembling that described in the present paper. This suggests that the invasion of the arterial intima by macrophages bearing cholesterol esters may be an example of a standard reaction pattern to certain higher alcohols.

The affinity for cholesterol is that of the vessel wall rather than that of the intima alone. In syphilitic aortitis, which favors the development of atherosclerosis, the invasion of the vessel wall by lipoid cells is not limited to entrance through the endothelium from the lumen but includes migration from the branches of the vasa vasorum in the thickened vascularized intima and in the media as well. This invasive attack from within and without tends to produce a higher grade of

20. Hueper, W. C.: Arch. Path. **31**:11, 1941.

21. Hueper, W. C.; Landsberg, J. W., and Eskridge, L. C.: J. Pharmacol. & Exper. Therap. **70**:201, 1940.

aortic atherosclerosis, particularly in the ascending aorta, than occurs in the absence of the syphilitic process.[22]

LOCAL PRODUCTION OF LIPOID CELLS

Thus far in this article I have considered only those cholesterol-bearing cells arising, as a part of a general process, from the liver and adrenals. Cells of this type may arise from other sources in the so-called reticuloendothelial system, such as the spleen, though the evidence indicates that the spleen is at best a secondary source of lipoid cells and is more important as a site of deposit. This is also

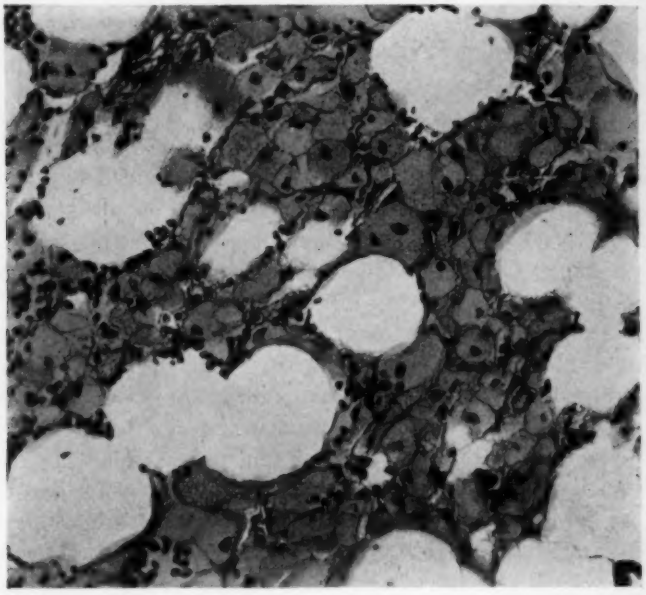

Fig. 18.—Lipophages in gastrohepatic omentum about a subacute abscess (human). × 250.

true of the marrow and the lymph nodes. The local production of lipoid cells is commonly seen following necrosis in the brain. The brain is rich in cholesterol and is a common commercial source of this substance. Necrotic exudates, whose cells are rich in cholesterol, may be surrounded and invaded by histiocytes, which engulf the cholesterol and contain it in ester form (fig. 18).

INTRACELLULAR ACTION ON CHOLESTEROL

Cholesterol-bearing lipoid cells may invade the intima of blood vessels even in infancy, and I have observed invasion of the intima of the coronary arteries of such cells in congenital heart disease in an

22. Leary, T.: New England J. Med. **223**:789, 1940.

infant aged 3 days.[23] The ordinary minor processes occurring in infancy and at puberty tend to be temporary and are terminated by the removal of the cholesterol through the action of fibroblastic cells.[24] In the fibroblastic cells the esters are broken down, presumably by an esterase. The fibroblasts come to contain fat drops, which tend to be large but are irregular in size. The fat is no longer anisotropic. The cholesterol is evidently in solution. In frozen sections stained with nile blue sulfate the contents are colored purple or blue in contrast to the contents of the persisting macrophages, which stain red. This indicates an excess of fatty acids in the fibroblasts. Hirsch [25] has shown that although human fat becomes saturated with cholesterol in 4 per cent solution, when oleic acid is added to human fat the mixture is capable of dissolving cholesterol up to a 13 per cent solution before saturation occurs. The combination of esterase action and increased fatty acid in the intimal fibroblasts apparently leads to solution of the cholesterol, and this is followed by the removal of the substance from the intima in youth. As the body ages, the power to remove cholesterol from the arterial intima in general progressively decreases. This power persists, however, even to old age, in the ascending aorta.

Similarly in the masses of lipoid cells which obstruct lymph vessels in the liver and adrenals there is a loss of the orderly arrangement of the droplets within the cells. The drops become larger and more uneven in size. Under nile blue sulfate staining the cell contents undergo changes in color toward the blue (fig. 19*A*). There is a loss of anisotropism (fig. 19*B*). A progression of color from red to purple can be followed in the cell masses, the red occurring in the cells in lymphatics nearest their lobular sources, the purple in those farthest removed from the lobules. When obstruction of outlets is marked, even the lipoid cells in the liver trabeculae may take a purple color. In this case the esterase action and the increase of fatty acid seem to arise within the lipoid cells themselves. The evolution of fatty acids and the solution of cholesterol after deesterification of the esters were found to occur only when the delivery of lipoid cells to the circulation was delayed, as in the remarkable lymphatic obstruction described.

COMMENT

From the evidence presented, the cholesterol in atherosclerotic lesions, both human and experimental, is carried into the arterial intima in phagocytic cells. Cholesterol is esterified in the liver and in

23. Leary, T.: Arch. Path. **17**:453, 1934.

24. The great differences in appearance of lipoid macrophages and branching fibroblasts which remove cholesterol from atheromatous lesions in youth led me to look on them as distinct cell types. Moen (J. Exper. Med. **61**:247, 1935) cultivated fibroblasts from single isolated migrating pleural macrophages and expressed the belief that macrophages can convert themselves into fibroblasts.

25. Hirsch, E. F.: Arch. Path. **25**:34, 1938.

the adrenals. Normally cholesterol esters are liberated from liver cells into the blood stream without the intervention of other cells. Under conditions of immoderate ingestion of cholesterol, excess esters are

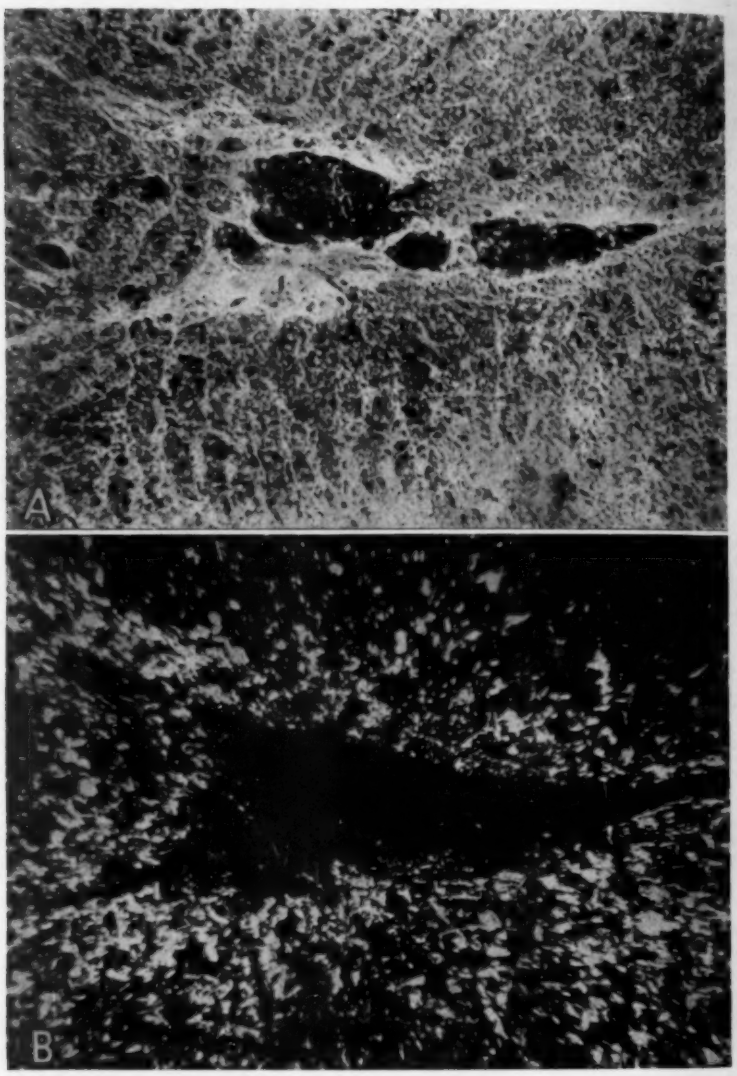

Fig. 19.—*A*, frozen section of liver, stained with nile blue sulfate. The esters have split, and the liver cells contain fat staining pink. Cholesterol has crystallized. *B*, same field viewed through a polariscope. The cell masses in the lymphatics contain few or no cholesterol crystals. Massed crystals may be seen in the surrounding liver tissue.

formed in addition to those set free into the blood stream. The overload is piled up in the cells of the liver and adrenals and becomes a burden.

The mere presence of cholesterol in excess in the blood is not adequate to cause atherosclerotic lesions. Rohrschneider [26] found up to 0.902 mg. of cholesterol per hundred cubic centimeters of blood on the twenty-ninth day after the feeding of the substance to rabbits began, and up to 1.208 mg. per hundred cubic centimeters on the thirty-eighth day, without aortic lesions. This period that elapses after the beginning of cholesterol feeding before lesions appear in the ascending aorta of the experimental rabbit (the site of the earliest lesions) is referred to herein as the latent period. It is terminated when phagocytic cells engulf the esters stored in the liver and adrenals as a foreign body, carry it from the organs through the lungs to the systemic circulation and invade the aortic intima. The invasion of the intima is apparently due to a positive chemotaxis, which is selective for cholesterol. Stresses favor the localization of the cells.

The lesion is not due to the mechanical introduction of free lipoids in the blood plasma and their precipitation in intercellular spaces. In the initial stages there is no inflammatory reaction. Edema, mucoid degeneration and lymphoid cell infiltration are all secondary phenomena. A focus of invasion once established apparently attracts other cells so that ultimately visible lesions are produced. As feeding of cholesterol continues, lesions may extend and fuse to make continuous processes.

The presence of cholesterol esters in the cells which have so invaded the intima stimulates a growth of connective tissue and the first step in the formation of a permanent atherosclerotic nodule is taken. In the arteries of youth, and in the ascending aorta even in age, a mechanism is active which serves to prevent the production of permanent nodules. The cholesterol is deesterified, is taken into solution in an excess of fatty acids and is removed from the intima. In some cases even in youth the stay of cholesterol may be long enough to stimulate some growth of fibroblastic cells, but collagen formation, if it occurs at all, is slight, and visible scarring does not take place save in extreme cases.

On the other hand, syphilitic aortitis not only inactivates the mechanism which removes cholesterol from the ascending aorta but renders the portions of the vessel which are affected more susceptible to lipoid cell invasion. As a result the degree of atherosclerosis produced is perhaps the highest met with under any conditions.

Once an atherosclerotic nodule has been started, if it is to be permanent, growth of fibrous tissue and scarring will follow. In human atherosclerosis the lesions progress slowly by intermittent accretions, requiring usually years to reach a dangerous stage of development. These stages of development as studied in human aortic lesions can be followed with considerable exactness.[10]

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26. Rohrschneider, W.: Virchows Arch. f. path. Anat. **256**:39, 1925.

In the causation of human and experimental atherosclerosis cholesterol and stresses are the important common denominators. Age, because of the time necessary for the recurrent accumulation of the effects of excess cholesterol, is important in a high per cent of human examples of the disease, though coronary sclerosis is met with as a cause of death in the third decade of life.[22] In the experimental animal one can overcome the time factor by continuous feeding of excess cholesterol. Sex is a factor in the human disease. The morbidity and the mortality from coronary sclerosis are low in women. The human female has apparently a more efficient cholesterol metabolic system than the male. This is perhaps because in pregnancy she is required to mobilize cholesterol for the needs of the fetus. A minor mobilization occurs with each menstruation. The sex factor can also be surmounted in the experimental animal by excessive feeding. Thyroid secretion is a deterrent factor with reference to atherosclerosis. It is recognized in human pathology that hyperthyroidism is accompanied by little or no atherosclerosis, particularly in the coronary arteries, even in advanced age. Hypothyroidism, on the other hand, is linked with advanced atherosclerosis. By adding thyroid preparations to the diet of cholesterol-fed rabbits it is possible to modify or prevent the production of atherosclerosis. Even this powerful agency can be overcome by increasing the dosage of cholesterol.

It is evident that atherosclerosis is a lipoidosis which, probably because of limited and intermittent excess dosage in man, tends to be restricted largely to the arteries. Only in unusual persons, in whom tolerance for the substance may be lower, is the lipoidosis more general, e. g., xanthoma formation. The great excess and the continuous dosage in the eperimental rabbit result more frequently in a wider distribution of cholesterol.

II. EXCESS CHOLESTEROL AS AN IRRITANT

Excess cholesterol esters are treated as particulate matter and are engulfed as such by phagocytic cells. A comparison of the effect of excess cholesterol with that of other forms of particulate matter reveals its irritant action. The commonest varieties of particulate matter in human tissues are the pulmonary dusts, which are for the most part relatively inert. Siderosis, chalicosis and even anthracosis may by the mere mass of the inhaled dust give rise to clinical manifestations, but their presence is in general of little importance. This is also true of most of the particulate matter injected intravenously in experimental animals.

There is one substance, however, which is an irritant, provoking a growth of fibrous tissue, whether inhaled by man or introduced into the

bodies of experimental animals. Silica and certain silicates (asbestos) are capable of producing high grade fibrosis of the lungs when inhaled, both in man and in experimental animals. Gye and Purdy [27a] demonstrated that silica sol (colloidal silica) would kill mice or guinea pigs on intraperitoneal injection in small doses. They established that for most laboratory animals the fatal dose was 100 mg. per kilogram. It was concluded that the silicon ion was the cause of toxicity. Daily intravenous injection of small doses led to increased activity of Kupffer cells and finally to fibrosis of the liver.[27b] In a later publication [27c] they reported that in chronic poisoning in rabbits the outstanding lesions were fibrosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of "chronic interstitial nephritis" in man.

Extensive studies with intravenous injection of silica crystals (powdered quartz) in suspension were made by Gardner and Cummings.[28] The larger particles (10-12 microns) were sifted out in the lungs. The particles of medium size (6-8 microns) were filtered out in the spleen. The finer particles of the order of 1 micron, which made up the mass of the suspended silica, were taken out of the circulation in the liver. As a result of their presence, a well marked cirrhosis arose in the liver within two years. A control series of rabbits received injections of aluminum oxide in suspension over a period of twenty-two months. At autopsy no evidence of stimulation of fibroblasts was found.

The lesions produced by the intravenous injection of silica sol consist in cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of human "chronic interstitial nephritis." It is of interest that chronic cholesterol poisoning in the experimental rabbit should tend to be associated with cirrhosis of the liver, enlargement of the spleen and renal changes resembling those of "chronic interstitial nephritis." Silica is a much more powerful irritant than is excess cholesterol, and there is a limit to the amount of it which can be introduced into experimental animals. Gardner and Cummings found that injury to the ear veins about the sites of injection made it difficult to carry out injections of the substance freely, and the general toxicity of silica sol restricted the use of this substance by Gye and Purdy. Cholesterol is a relatively bland material in rabbits up to a dosage by catheter of about 1 Gm. per day. Beyond that point diarrhea occurs, with death following within a few days in some cases. The total amount of cholesterol fed by catheter may reach 250 Gm. or more if the dosage is small. However, the end results of such feeding involve over a period of years widespread lipoidosis and include in many cases infiltration of most organs and various tissues.

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27. Gye, W. E., and Purdy, W. J.: (*a*) Brit. J. Exper. Path. **3**:75, 1922; (*b*) **3**:86, 1922; (*c*) **5**:238, 1924.

28. Gardner, L. U., and Cummings, D. E.: Am. J. Path. **9**:751, 1933.

Silica and excess cholesterol have much in common. They are both difficult of metabolism. They tend to be held in the tissues for long periods, once they have gained entrance. Long stay in tissues is necessary for the production of fibrosis. Silica owes its toxicity to the silicon ion, according to Gye and Purdy. The similar toxic effect of excess cholesterol probably depends on chemical action.

LATE LESIONS OF SPECIFIC ORGANS OR TISSUES

Arteries.—Just as it is possible to follow the sequence of progressive changes in the lesions of atherosclerosis in human vessels, particularly the aorta,[10] so is it possible to note the similar progressive changes in the arteries of the experimental rabbit. The sequence begins with lipoid cells invading the subendothelial layer of the intima. The next step is minor fibrosis, and the deeper invasion of the gradually thickening intima by the lipophages. In both human and experimental lesions these cells may even invade the media, usually in focal regions in smaller vessels, such as the coronary arteries. With the deeper invasion of the intima there is an increase in fibrosis and as time passes a slow elimination of the lipophages and the cholesterol from the lesion (fig. 20 *A*). The fibrous lesion is at first cellular. Gradually more and more collagen is formed. With the increase of collagen the cells undergo wider separation and many cells disappear. A late stage is marked by hyaline change in the fibrous tissue (fig. 20 *B*). Regions of necrosis may arise to be followed by calcification (fig. 21 *A*). Calcification is less common and less marked in the rabbit than in human atherosclerosis. This is probably due in considerable part to the age factor, since experimental rabbits are usually killed long before they reach advanced ages. The feeding period in the rabbit is usually continuous and limited to a period of months. In rabbits in which feeding of cholesterol in small doses is terminated in six months at most, the arterial lesions usually go through the changes up to hyaline fibrosis and progress no further.

The repair of arterial lesions in the younger animals as time elapses after feeding is stopped is more perfect than that seen in man. The fibrous tissue which is formed narrows the lumen of the vessel permanently, but the connective tissue of the lesion is often less dense than in human lesions. Probably for this reason but also because the animals lead a highly sedentary life in their cages, thrombosis is not common. Sudden deaths of the types associated with obstruction of the coronary arteries may arise, but they are usually due to coronary insufficiency and not to thrombosis. Atherocheumas may be produced, in spite of statements that they do not occur in the experimental rabbit. I have recently reported with Dr. Soma Weiss[29] the death of a rabbit from

29. Leary, T., and Weiss, S.: Arch. Path. **29**:665, 1940.

dissecting aneurysm of the aorta arising from rupture of an atheromatous ulcer, a lesion which is also said not to occur in the rabbit. Thrombosis at the site of the ulcer and thrombosis, probably of the

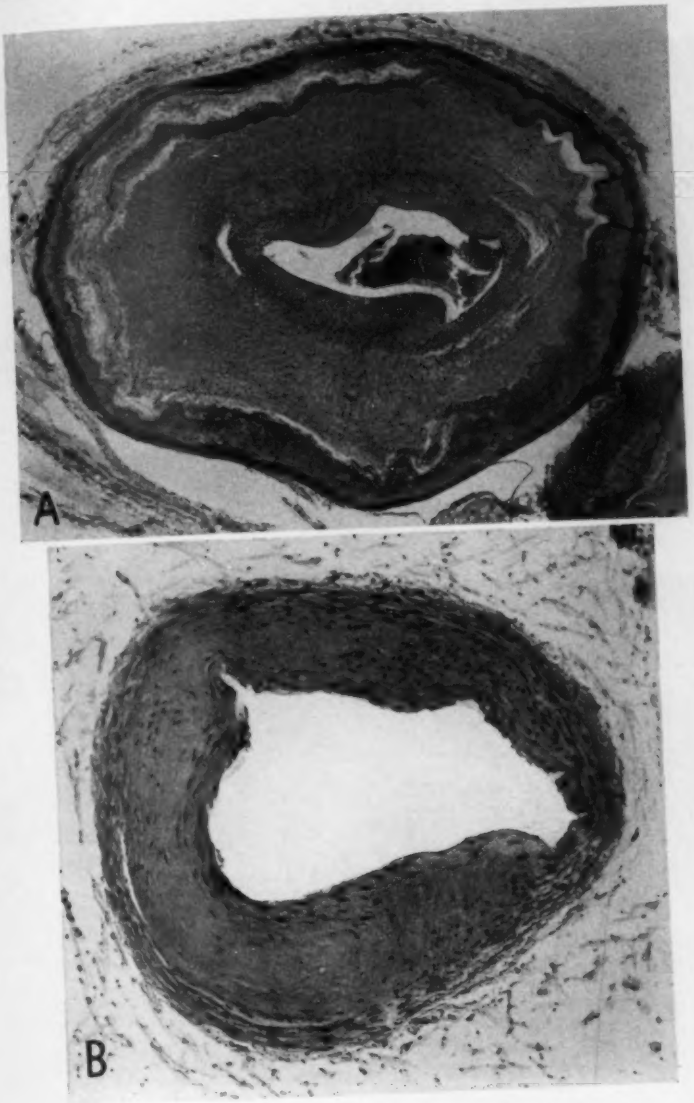

Fig. 20.—*A*, section of a carotid artery of a rabbit. There are advanced fibrosis and thickening of the subendothelial layer of the intima in general. The process is still active; the more central layers are still cellular. × 33. *B*, coronary artery of a rabbit, showing a late process with thickening and hyalinization of the wall. × 130.

marantic type, in a greatly narrowed carotid artery were found in this animal.

Thus lesions corresponding in type and in their method of progression to the human arterial processes have been produced in the experimental

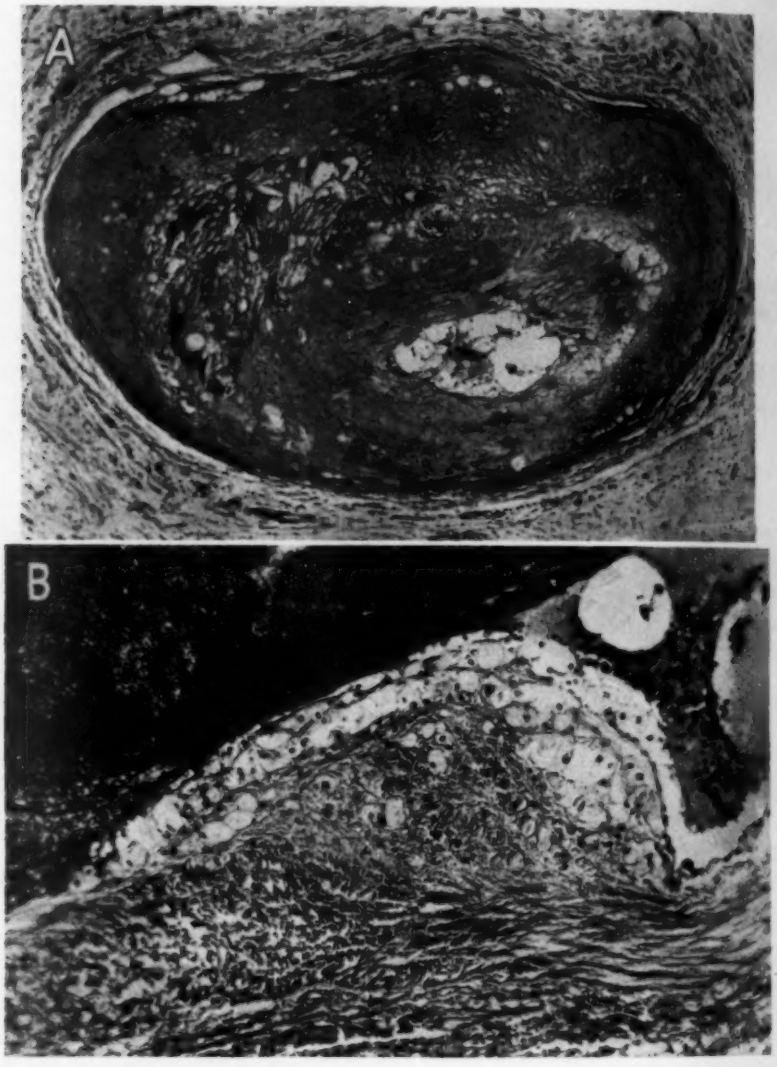

Fig. 21.—*A*, branch of a rabbit's coronary artery, with obliteration of the lumen, hyaline fibrosis and necrosis. A region of calcification is sharply outlined at the left, with slits for cholesterol crystals. × 60. *B*, intimal lesion. Older fibrosis is shown in the lower portions of the lesion; recent invasion of lipoid cells, beneath the endothelium. The section is from a female rabbit fed 67 Gm. of cholesterol between Sept. 22, 1937 and March 9, 1938 and 78.4 Gm. of cholesterol between June 1, 1939 and Feb. 12, 1940. × 220.

rabbit. The differences which have been mentioned between human and experimental lesions are largely dependent on differences in the manner of feeding cholesterol, i. e., in one short continuous sequence in the experimental rabbit but in intermittent dosage over a period of years in the human being. These differences have been overcome in part by feeding cholesterol for a limited time, adequate to produce lesions, and renewing the cholesterol additions to the diet after an interval without cholesterol (fig. 21 *B*).

Recently attention has been directed to the occurrence of what may be called a subacute form of focal myocarditis. Coronary thrombosis with infarction is associated with necrosis not only of muscle fibers

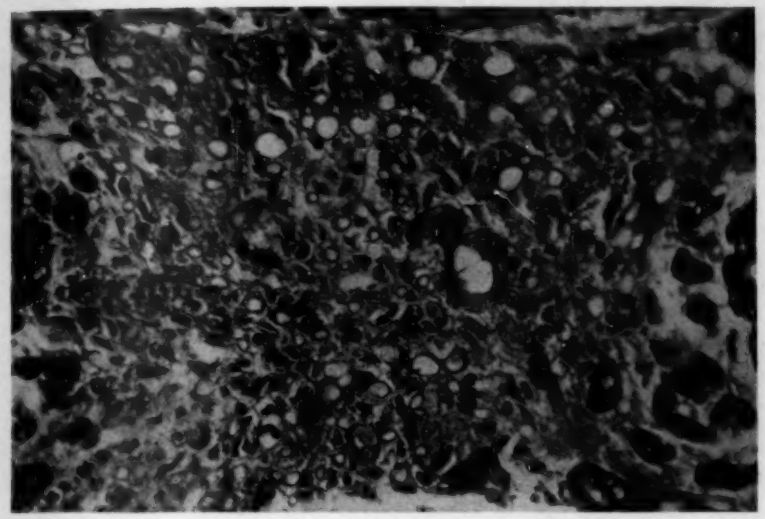

Fig. 22.—Early subacute focal myocarditis. Remnants of some of the muscle fibers persist in places. The section is from a rabbit. × 470.

but also of the intermuscular connective tissue, i. e., total necrosis followed by an acute inflammatory reaction. At the other extreme so-called chronic vascular myocarditis is marked by slow nutritional atrophy and necrosis of the high grade muscle fibers with repair and scarring. The subacute type of myocardial change is probably dependent on coronary spasm continued long enough to lead selectively to acute necrosis of muscle fibers, leaving the intermuscular connective tissue intact. This condition was reported by Roesler and Soloff,[30] and later it was discussed by Lisa and McPeak [31] under the title "Acute Miliary Infarction of the Heart." Since the lesion is not a true infarction I prefer

30. Roesler, H., and Soloff, L. A.: Ann. Int. Med. **9**:477, 1935.
31. Lisa, J. R., and McPeak, E.: Arch. Int. Med. **65**:919, 1940.

the term "subacute focal myocarditis." Of rabbit hearts showing advanced coronary sclerosis, lesions of subacute focal myocarditis have been observed in 2. This is the first recorded production of this lesion in the experimental animal (fig. 22).

The Liver.—The early stages of hepatic esterification of cholesterol and the storage of the ester in liver cells have been illustrated in part I. Important with reference to terminal effects is the result of the lymph blockade within the lobules. The persistence of lipophages which cannot escape from the centers of the lobules stimulates a growth of connective tissue. The central liver cells are compressed and undergo atrophy,

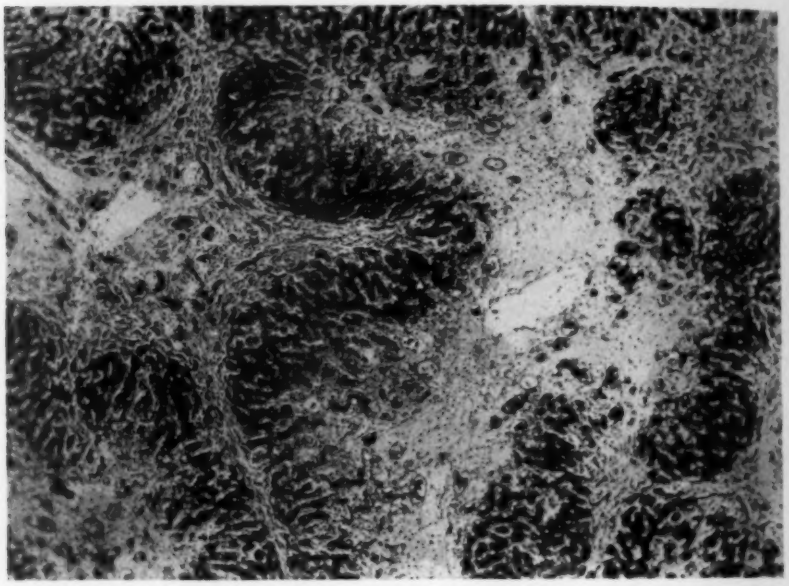

Fig. 23.—Rabbit liver showing early cirrhosis. In the mid-region may be seen the center of a lobule with necrosis of liver cells and replacement of these cells by cellular connective tissue which is rich in lipophages. To the left, the portal space contains many new bile ducts. × 56.5.

while many cells disappear. At the same time there is apparently a stimulation of the liver cells in the peripheries of the lobules, with the formation of new bile ducts (fig. 23). As the liver process ages in the cirrhotic liver, the fibrous tissue in the lobular centers appears to be slowly extruded through the proximal portions of the lobules, as though by a process of inversion of the lobule, and a quite typical portal cirrhosis of the liver is the end result. This same effect is seen in experimental cirrhosis due to carbon tetrachloride, in which the destructive lesions are largely limited to the centers of the lobules. In the cholesterol-fed

animal there may result marked gross lobulation of the organ (fig. 24 *A*). There is often a considerable increase in peritoneal fluid at death, but no degree of ascites comparable to that occurring in man has been observed. Neither have esophageal varicosities been found.

The sequence of events in the rabbit's liver appears to be as follows: Cholesterol in solution in the fats comes to the liver from the intestine through the portal vein. The cholesterol is esterified and passed from the liver cells into the circulation. When received in excess, the esters are stored. Usually the removal of the excess esters by Kupffer cells is successful within a period of a few months after feeding is stopped. Under these conditions the return of the organ to normal may be complete. In some cases there may be a relatively minor increase of interlobular connective tissue. When there is obstruction to lymphatic outflow, and cells carrying esters are held up in the centers of lobules, the stimulation to connective tissue will result in definite high grade cirrhosis. In some cases, if the animal lives long enough, a type of healed inactive cirrhosis may be the end result. There is minimal lymphoid cell infiltration of the tissue in the portal spaces. The newly formed bile ducts may be taken up into the lobules. Apart from the variable size of the lobules and the increased interlobular connective tissue there is little evidence of the active process which must have been present.

The Adrenals.—Like the liver, the adrenals after cessation of the ingestion of cholesterol tend gradually to shrink in size as the excess cholesterol is eliminated from the organ. The return to normal both in size and in appearance is constant. The newly developed lymphatics in the medulla may persist for a long period.

The Lungs.—Apart from atherosclerosis of the pulmonary arteries, which is quite constant, the lungs show at most minor foci of lipophage deposit in the subpleural connective tissue. These deposits tend to disappear in time.

When cholesterol in oil is delivered into the trachea through error in feeding, there will result lipoid pneumonia. The alveoli are filled with lipophages together with fibrin, some lymphoid cells and polymorphonuclear leukocytes. If the amount introduced is small, the process may be limited to single or small groups of lobules, usually in the lower portions of the lungs. If the amount is large, the process tends to be lobar in character and to be accompanied by massive fibrinous and lipoid pleuritis, which may lead to death of the animal.

The Spleen.—During the ordinary period of cholesterol feeding the spleen shows little or no enlargement. After the feeding period, however, the organ undergoes progressive enlargement and may ultimately increase in size to several times normal (fig. 24 *B*). Lipophages may

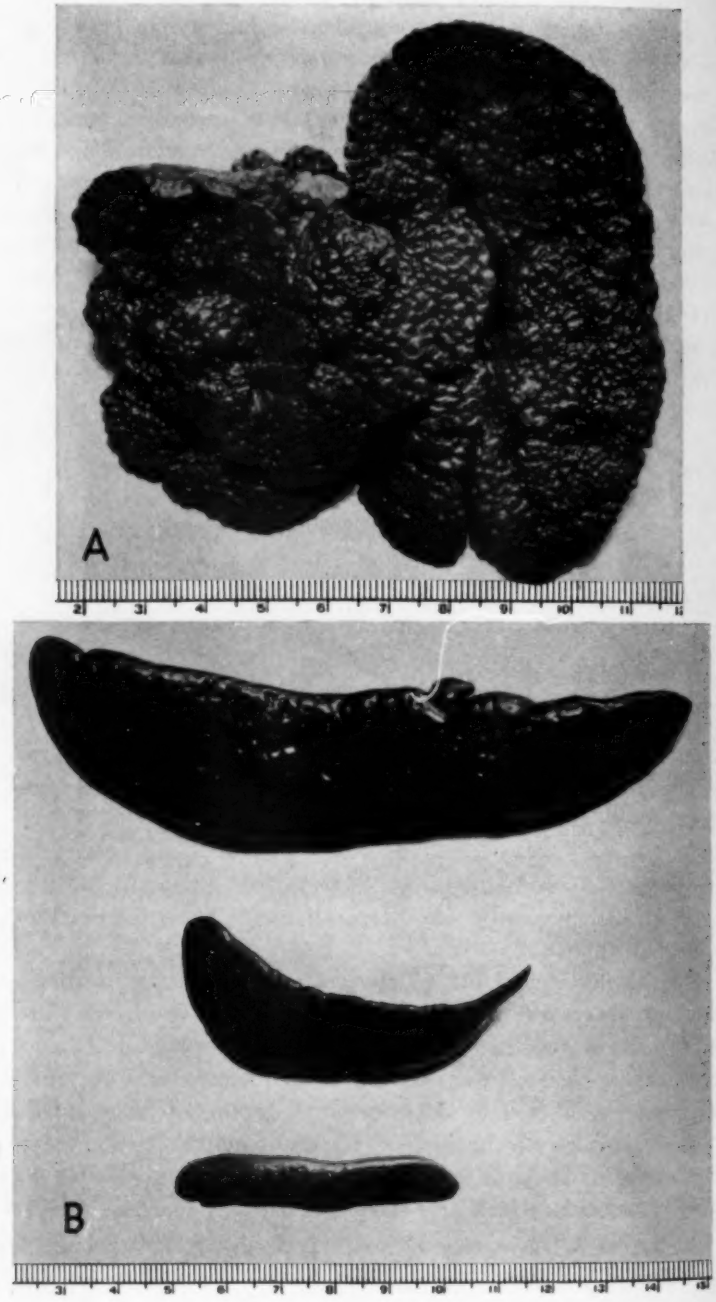

Fig. 24.—*A*, portion of the liver of a rabbit, showing nodular cirrhosis—portal type. *B*, secondary enlargement of the rabbit spleen. The lower spleen is a normal organ for comparison.

be present in numbers in the sinuses, and the blood in the veins may contain masses of lipoid cells in the relatively early period. Hemorrhages may occur, and lipophages also carrying blood pigment may abound in the sinuses. As time passes, the lipophages come to rest in the interstitial spaces (fig. 25), notably beneath the capsule. The deposit appears to be permanent, since the cells filled with lipoid may be found here years after feeding has ceased.

The Kidneys.—The kidneys excrete cholesterol in small amounts under normal conditions. It is probable that in the experimental rabbit an unusual effort is made to excrete the excess of cholesterol. This results in deposits of cholesterol in the tubular epithelium in the convoluted tubules and particularly in Henle's loops. Frozen sections of

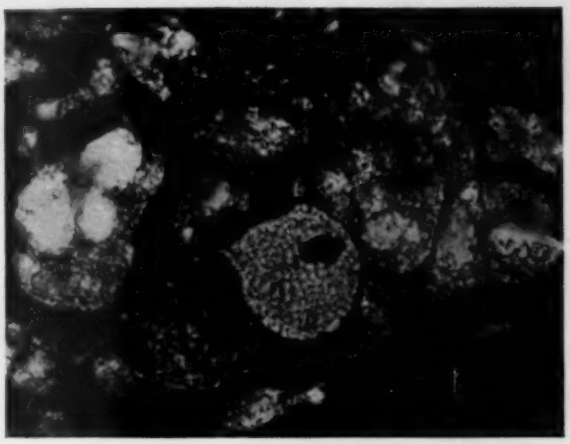

Fig. 25.—Lipophages in spleen pulp from a rabbit. × 800.

the kidney in excretory activity disclose masses of lipoid in the tubular epithelium of Henle's loops. Under the polariscope the lumens of tubules whose cell contents stain deeply with sudan IV contain anisotropic crystalline material. In the cells in the proximal convoluted tubules fine fat granules are found. In paraffin sections these cells are swollen, pale and clear. In the glomeruli occur fine granules staining with sudan IV, and cells of the distal convoluted tubules contain fine granules.

Apart from the evidences of excretion or attempted excretion in the nephron, lipoid cells appear in numbers in the pyramids about the arterioles and veins and in the intertubular connective tissue. As the cells increase in numbers, their nutrition apparently suffers, and necrosis sets free the contained esters. The esters are split, and the cholesterol recrystallizes in relatively large crystals. These become matted into

dense masses, which compress tubules and blood vessels. This is associated with great increase in the size of the kidney. The number of functioning tubules diminishes as the cholesterol crystals collect and the pressure is increased. The cortex is gradually squeezed into a narrow

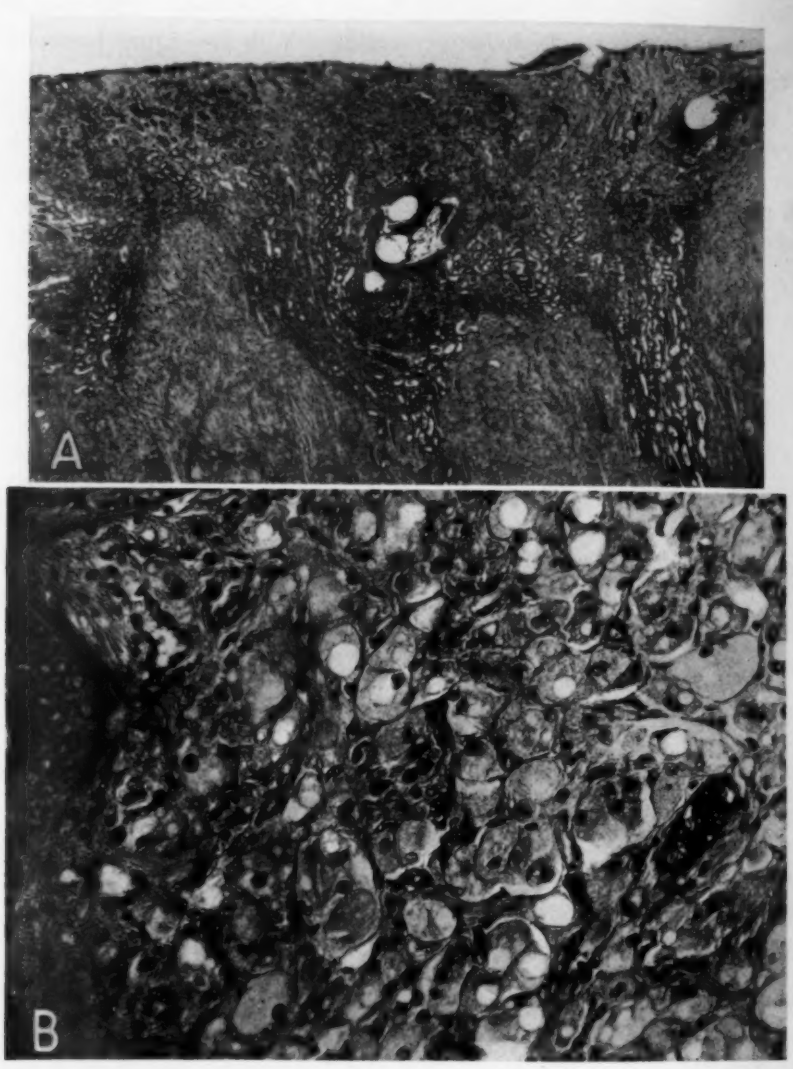

Fig. 26.—*A*, section of rabbit kidney from an advanced late lesion. Extending upward from the pyramid are masses of cholesterol crystals embedded in fibrous tissue. The narrowed cortex shows fibrosis, with few nephrons, and diffuse lymphoid cell infiltration. × 30. *B*, xanthoma occurring spontaneously on the back of the neck of a cholesterol-fed rabbit. Note the derma distended by lipoid cells in interstitial spaces and proliferation of fibroblasts. × 244.

layer. Not only is it thinned, but glomeruli and tubules become fewer, connective tissue is increased, lymphoid cell infiltration occurs and a picture resembling chronic vascular nephritis is the end result (fig. 26 *A*). As is common in human autopsies, the main renal arteries apart from the proximal 0.5 cm. show little or no evidence of atherosclerosis. On the other hand, the arteries and arterioles within the kidney are the site of cholesterol deposits quite generally.

The Skin and Supporting Tissues.—Attempts to reproduce xanthomas in the experimental rabbit began with the belief that hypercholesteremia and traumatism were necessary for their production. Anitschkow [32] after feeding rabbits cholesterol to the point that well marked hypercholesteremia developed injected subcutaneously collodion or turpentine and found that foam cells tended to congregate in the lesions so produced. Schaaf [33] fed hydrous wool fat to rabbits and traumatized the animals physically by placing clamps on their necks and chemically by injecting lipoid mixtures. Furthermore, hepatic disturbances were provoked by the use of roentgen radiation, arsphenamine or paratoluenediamine. Rusch and his associates [34] produced massive xanthomas of the legs and feet in rabbits fed cholesterol. However, 6 of their rabbits were exposed to ultraviolet rays daily, and most of the animals were inoculated with Shope papilloma virus. It was concluded that xanthomas were produced in animals as the result of hypercholesteremia alone without traumatism. The use of ultraviolet rays, which Ruffo [35] has demonstrated to cause an increase of cholesterol in the exposed skin, and the fact that papillomas developed on the legs of some animals weaken the proof that traumatism did not play a part in the development of xanthomas, particularly as these lesions were limited to the feet and legs, which are likely to be traumatized in ordinary use.

In the animals in my series which have been permitted to live for years after cholesterol feeding was stopped I have observed the production of xanthomas of the back of the neck and the front of the chest. The process on the back of the neck was localized and was first observed because of the depilation of the region, exposing a moderately thickened granular opaque yellow skin. A biopsy specimen fixed in Zenker's fluid showed foam cells in quite closely packed masses in the derma and extending into the subcutaneous tissue (fig. 26 *B*). Comparison with a human xanthoma obtained through the aid of Dr. Siegfried J. Thann-

32. Anitschkow, N.: Arch. f. Dermat u. Syph. **120**:627, 1914.

33. Schaaf, F.: Arch. f. Dermat. u. Syph. **175**:279, 1937.

34. Rusch, H. P.; Baumann, C. A., and Kline, B. E.: Arch. Path. **28**:163, 1939.

35. Ruffo, A. H.: Bol. Inst. de med. exper. para el estud. y trat. del cáncer **9**:30, 1932.

hauser made it evident that it would be impossible in high power fields to distinguish the human from the rabbit lesion. The conformation of the epithelial surface layer was the only means of discriminating. Since that time diffuse xanthoma formation with marked thickening of the skin over the upper part of the chest has been observed in 2 animals. It is remarkable that xanthomas of the feet and legs have not been observed in any of my animals, some of which have shown diffuse lipoidosis, including massive invasion of the eyes.

The lesion on the back of the neck ultimately disappeared, leaving little trace save perhaps a slight increase of connective tissue in the derma.

Anitschkow expressed the belief that xanthoma formation was prone to occur in dense tissues, such as the derma, in which interference with lymphatic drainage might cause concentration of cholesterol and its precipitation. After the precipitation, local macrophages engulfed the cholesterol and produced the characteristic lesion. This is merely an application to the derma of the Aschoff concept of the precipitation of free cholesterol esters in the arterial intima and its seizure by locally produced cells. From my observation the lesions are due to the transport of cholesterol esters in macrophages into the derma and subcutaneous tissues. The lipoid may be removed from human or rabbit lesions with a restitution to the normal save for a minor increase in connective tissue. The mechanism of removal is probably that described in the arteries and the lymphatics.

One objection to the theory that density of tissues is necessary for cholesterol deposit is the occurrence of quite permanent deposits in soft tissues, such as the spleen, kidneys, ovaries and testicles, as well as in the ciliary processes and in the iris. It is true, however, that the most permanent deposits of cholesterol tend to occur in dense tissues, such as scar tissue, the derma, the cornea and similar structures. Slowing of the metabolism because of the density and the inadequate circulation probably account for the delays in the removal of the cholesterol from these sites. For the same reasons, silica crystals tend to persist indefinitely in scar tissue. The massing of compacted cholesterol crystals into tophus-like bodies which occurs in human xanthomas of long standing has not been observed in the rabbit.

There is a sharp distinction between the organs which normally esterify or metabolize cholesterol and the other organs and tissues, with reference to the permanent deposit of excess cholesterol. During the period of ingestion the largest collections of the substance occur in the liver and the adrenals. When the dosage is excessive, cirrhosis of the liver may be produced, and the stay of excess cholesterol in the organ may be prolonged. However, ultimately the liver and

adrenals tend to be cleared of the excess. The lungs, in which small interstitial deposits of lipophages may occur, in addition to lesions of the pulmonary arteries, also tend to become free of the substance apart from the vessels. Once cleared, the liver, lungs and adrenals remain free of an excess of cholesterol, except for the arteries in these organs.

In practically all other organs and tissues cholesterol storage occurs, usually after the period of ingestion, though to some degree during the later stages of the period, depending on time and dosage. Mobilization of the cholesterol by lipophages may continue for months or years after ingestion ceases. One may observe in the iris and cornea of the rabbit a progressive accumulation of opaque cholesterol as late as two or three years after ingestion has ceased.

During the period of ingestion and until the liver and adrenals have been freed from the excess cholesterol esters the transport of esters is almost exclusively the function of Kupffer cells and their analogues in the adrenals. After the liver and adrenals have been freed from cholesterol, the esters are carried in lipophages, some of which may have originated in the liver or the adrenals but most of which are probably histiocytes of local origin in tissues in which older lesions are undergoing fibrosis with the removal of cholesterol to new sites.

The spleen, kidneys, subcutaneous tissues, tendons, irides, corneas, lymph nodes and bone marrow, together with the ovaries and testicles, are tissues in which more permanent deposits of cholesterol usually occur in the experimental animal.

COMMENT

In part II attention has been drawn to the close analogy between the effects of excess cholesterol and silica when the latter is introduced by intravascular injection into rabbits in colloid or other suspension. These two substances, practically alone among particulate matters, are benign enough in small but adequate doses to produce a chronic (instead of an acute) disease, but irritant enough to provoke fibrosis of the liver, enlargement of the spleen and changes in the kidney resembling those of "chronic interstitial nephritis," to use the phraseology of Gye and Purdy.

The tendency of the organs which have to do with cholesterol esterification (liver and adrenals) or with cholesterol metabolism (lungs) to free themselves permanently of the substance in the period following ingestion is described. If excess cholesterol esters are prevented from leaving the liver by lymphatic obstruction a true cirrhosis may result. Even in this event the liver once freed of excess cholesterol may undergo healing. The spleen and kidneys among the larger organs are secondary depositories of cholesterol. The affinity of

cholesterol for the arterial intima is the source of atherosclerosis. In man repeated accretions in the arterial lesions may ultimately produce insufficiency of smaller vessels or may lead to thrombosis. In the experimental rabbit cholesterol feeding is carried out in a continuing sequence which is stopped abruptly. In spite of these differences in methods of production the arterial lesions of the rabbit and man are comparable.

The excessive dosage in the experimental rabbit overloads the economy of the animal with a substance difficult of excretion. As a result, more general lipoidoses arise more frequently than in man. Among these the cutaneous and subcutaneous xanthomas correspond closely to human lesions.

SUMMARY

Evidence is presented:

That atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells, which first appear in the intima of the arterial wall.

That cholesterol is esterified in the liver as directly observed in the experimental rabbit.

That cholesterol when fed in excess to rabbits is deposited in the form of esters in the cells of the liver and adrenals.

That the esters as they accumulate in excess become a burden and are removed from these organs by Kupffer cells in the liver and their analogues in the adrenals.

That the cholesterol esters are engulfed as particulate matter by these cells.

That these cells, now lipoid cells, escape from the liver and adrenals through the blood and lymph systems and may produce obstruction in the lymph sinuses.

That lipoid cells, having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses but is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters.

That the latent period after the beginning of cholesterol feeding in the rabbit and before aortic lesions appear is dependent on the production of esters in excess and their transport, as indicated in paragraphs 2 to 7 inclusive.

That lipoid cells possess the power to split cholesterol esters and bring the substance into solution in an excess of fatty acids.

That excess cholesterol esters are akin to silica in their irritant character. Both are difficult of metabolism, tend to stay long in tissues and stimulate a growth of connective tissue.

That intravenous silica and cholesterol esters, practically alone among particulate matters, tend to cause in rabbits cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of chronic "interstitial" nephritis.

That human atherosclerosis is associated with intermittent accretions of excess cholesterol esters in contrast to the continuous accretions in the rabbit fed cholesterol. That the differences in the appearance of atherosclerotic lesions in the two species are due in great part to differences in the manner of feeding. Diffuse lipoidosis is more common in the experimental rabbit, partly for the same reason.

The accepted criteria for the establishment of a causal relation between a given agent and a disease are embodied in Koch's laws. Since animals are not susceptible to all human infections, or because evident parasites cannot be cultivated, or for other reasons, various compromises have been made with these postulates. However, the evidence of a causal relation is most complete when Koch's laws can be satisfied.

In the causation of atherosclerosis the principles of Koch's laws can be fulfilled. Excess cholesterol is always present in the active stages of human atherosclerosis. It can be identified in the lesions as definitely as can the bacterial or other parasitic agents producing infections. It can be extracted from the lesions. Human arterial lesions can be reproduced experimentally by its use with more exactness than the lesions of many human infections can be reproduced by the introduction into susceptible animals of their recognized causal agents. It can be identified in and extracted from the experimental lesions.

Stresses determine the localization of lesions and influence the degree of the sclerotic processes. The efficiency of cholesterol metabolism is modified by sex and thyroid factors. Age (time plus thyroid deterioration) and heredity are also contributing elements.

LIPOIDS IN THE KIDNEY

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CINCINNATI

The histologic demonstration of fatty deposits, some of which were doubly refractile, in the kidneys in conditions clinically diagnosed as "lipoid nephrosis" suggested a comparative study of the quantity, distribution and refractility of stainable lipoids in a series of kidneys obtained at necropsies and representing various pathologic conditions.

The present study is essentially histologic in character. No attempt is made to determine the chemical identity or to recognize the individual characteristics of the various tissue lipoids. "Lipoid" is a term of indefinite significance. For present purposes it will be used as a term embracing the entire group of fatlike substances occurring in tissues, including true fats, fatty acids, phosphatides, cerebrosides, sterols and their combinations.

Michaelis [1] introduced scarlet red as a means of staining lipoid. This staining substance and the related substance sudan III are two synthetic dyes which stain fat in a purely physical way, entering and remaining in fat droplets because they are more soluble in fat than they are in water or in alcohol. Simple alcoholic solutions of scarlet red, while sometimes (especially if heated solutions are used) staining all of the tissue lipoids demonstrable by any other method, ordinarily fail to stain many fat droplets. The use of scarlet red in strongly alkaline solution, as recommended by Herxheimer,[2] is distinctly advantageous in that it stains all lipoids but does not stain other substances which might be capable of reducing osmium tetroxide. The alkali probably increases the effectiveness of the dye by causing liberation of certain fatty acids and formation of mixtures of fatty acids and other lipoids which more readily absorb the dye. Bullard [3] expressed the belief that many of the fatty droplets left unstained by simple alcoholic solutions of scarlet red but stained by the alkaline solution are made up of neutral fat.

From the Department of Pathology of the University of Cincinnati and the Cincinnati General Hospital.

1. Michaelis, L.: Virchows Arch. f. path. Anat. **164**:263, 1901.
2. Herxheimer, G.: Deutsche med. Wchnschr. **27**:607,1901.
3. Bullard, H. H.: J. M. Research **27**:55, 1912.

The polarizing microscope is an essential unit in the armamentarium for the study of the tissue lipoids. Mettenheimer (cited by Aschoff [4]) introduced the use of crossed Nicol prisms in the differentiation of certain fatty substances in tissues. The refractile (anisotropic) lipoids consist chiefly of cholesterol esters, and these are frequently mixed with varying quantities of phosphatides, fatty acids, soaps and neutral fats.

CONCEPTS OF FATTY CHANGES IN THE KIDNEY

In most instances the amount of fat in a kidney showing fatty changes is found equal to or less than the normal amount. The substance of an average normal kidney is about 18 per cent lipoid. A kidney showing "fatty degeneration" may be found to contain less than 16 per cent lipoid, while a kidney with a 23 per cent lipoid content may not show any fat whatever by staining methods (Leathes [5]). However, an actual increase in the amount of cholesterol ester in the kidney probably occurs in so-called lipoid nephrosis. The most characteristic morphologic evidence of "lipoid nephrosis" seems to be the deposit of anisotropic lipoid commonly found in the epithelium of the convoluted tubule. Gerard and Cordier [6] attacked the problem of the origin of this deposit by experiments utilizing a certain type of salamander. The kidney of this type of salamander is peculiar in that certain renal units communicate with the body cavity so that fluid contained within the latter may enter the convoluted tubules without necessarily passing through the glomerular filters. Other, closed nephrons do not possess this communication with the body cavity. Injections of fluid containing cholesterol into the body cavity resulted in the deposition of cholesterol in the epithelium of the open tubules but not in that of the closed tubules. Induced hypercholesteremia was impotent in causing deposition of cholesterol in the tubular epithelium until it was aided by injections of egg albumin. With the production of albuminuria, cholesterol became demonstrable in the epithelium of the closed tubules. The data obtained support the theory that cholesterol deposition in the renal epithelium can occur only after damage to the glomeruli and results from the reabsorption of cholesterol from the fluid contained within the lumen of the tubule. Popper [7] used the fluorescence microscope to study fat deposition in the kidney and described the presence in diseased kidneys of acetone-soluble fluorescent bodies, identified as vitamin A. This substance was never found in normal kidneys. It was found in largest amounts in "lipoid nephrosis" and

4. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924, p. 85.

5. Leathes, J. B.: Lancet **1**:95, 1906.

6. Gerard, P., and Cordier, R.: Arch. internat. de méd. expér. **8**:225, 1933.

7. Popper, H.: Proc. Inst. Med. Chicago **13**:331, 1941.

always in association with albuminuria. Popper concluded that the presence of vitamin A in the tubular epithelium is apparently due to reabsorption, the pathologic process being the escape of this lipoid through the glomerular filter as a result of increased permeability of the glomerular loops.

Much confusion exists in the literature as to the usage of the term "lipoid nephrosis."

If the demonstration of anisotropic lipoid deposited in the substance of the kidneys, usually in the tubular epithelium, is to be accepted as the sole criterion, the condition may be said to occur rather frequently, not often in pure form, but associated with such renal lesions as amyloidosis and diffuse glomerular nephritis. Lipoid nephrosis in this sense is looked on as nothing more or less than a reflection of increased permeability of the glomerular filter, regardless of cause (G. Fahr [8]).

Opposing this point of view are those clinicians and pathologists who consider "lipoid nephrosis" to be a specific disease entity characterized by cyclic edema, scanty urine, albuminuria, hypercholesteremia, reversed albumin-globulin ratio, lowered total serum globulin and presence of anisotropic lipoids in the urine but without elevation of the blood pressure, impairment of renal function, appearance of blood in the urine or detectable morphologic evidence of glomerular disease, although anisotropic lipoid is to be found in the tubular epithelium (T. Fahr [9]; Murphy and Warfield [10]; Leiter [11]). The diagnosis of "pure lipoid nephrosis" is made much more frequently by the clinician than by the pathologist. Cases clinically diagnosed as instances of "pure lipoid nephrosis" are very commonly found by the pathologist to be instances of diffuse glomerulonephritis in the subacute phase.

The theory has been advanced by Shapiro [12] that "lipoid nephrosis" is primarily not a disease of the kidney but a disturbance of lipoid-protein metabolism, a "lipoid-protein" diabetes, the kidneys being involved only as organs that actively excrete the products of the disturbed metabolism. However, a bilateral renal lesion closely resembling "lipoid nephrosis" is reported to have been produced experimentally in dogs by roentgen radiation (Bollinger and Laidley [13]; Bollinger and Earlham [14]). The experimental work of Gerard and Cordier in support of the theory that deposition of anisotropic lipoid in the renal epithelium can occur only after the glomeruli have suffered injury has been mentioned.

8. Fahr, G.: Am. J. M. Sc. **134**:449, 1937.
9. Fahr, T.: Virchows Arch. f. path. Anat. **239**:32, 1922.
10. Murphy, F. D., and Warfield, L. M.: Arch. Int. Med. **38**:449, 1926.
11. Leiter, L.: Medicine **10**:135, 1931.
12. Shapiro, P. F.: Arch. Int. Med. **46**:137, 1930.
13. Bollinger, A., and Laidley, J. W. S.: M. J. Australia **1**:136, 1930.
14. Bollinger, A., and Earlham, M. M. S.: J. Path. & Bact. **34**:603, 1931.

Material collected at necropsy in 40 cases presenting clinical evidences that justified the diagnosis of "lipoid nephrosis" was subjected to study by E. T. Bell.[15] In only 6 of these 40 cases was he unable to detect visible alteration in glomerular structure. In 19 cases the glomerular lesion was found to be a thickening of the capillary basement membrane, a thickening which Bell called "membranous glomerulitis." In 4 of these cases the lesion had resulted in such marked narrowing of the glomerular capillaries that uremia developed. The remaining 15 cases presented 6 examples of typical "chronic proliferative glomerulonephritis" and 9 instances of a mixture of proliferative and membranous glomerular lesions, the latter being predominant. According to Bell, 6 cases of "pure lipoid nephrosis" were instances of early "membranous glomerulitis" with the lesions not yet sufficiently developed to be morphologically detectable; the patients were young children. He concluded that "lipoid nephrosis" is a glomerular and not a tubular disease, that it is a form of glomerulonephritis in which the glomerular capillary walls are injured and become permeable to the plasma proteins and that when in a patient with "pure lipoid nephrosis" hypertension and uremia develop no new disease is superimposed—there is simply progressive thickening of the glomerular capillary basement membrane.

MATERIALS AND METHODS

Kidney tissues from 430 routine necropsies were fixed in 4 per cent neutral formaldehyde. The freezing microtome was used for sectioning. An attempt was made to cut the tissues so as to obtain representative portions of medulla and cortex in each section. A saturated solution of scarlet red in 70 per cent alcohol, to which 2 per cent of sodium hydroxide had been added, was used for staining. Preliminary to staining, the intact sections were placed in tap water. From this bath they were dipped for approximately three seconds into 70 per cent alcohol and then placed in the scarlet red solution. In order to minimize evaporation, staining was done in tall narrow test tubes. Into each tube about 3 cc. of the clear supernatant saturated stain was pipetted from the stock bottle immediately before staining. After the sections had remained in the dye for two minutes, they were washed in a second solution of 70 per cent alcohol for approximately three seconds in order to remove excess stain and were then floated out on tap water. Some sections were taken directly into the distilled water mounting bath. Other duplicate sections were counterstained with Harris' hematoxylin for three minutes, washed in tap water and placed in distilled water for mounting. The sections were floated out on clear glass slips, blotted and mounted in Kaiser's glycerin jelly.

In many instances serial frozen sections were stained with hematoxylin and eosin. In all cases the routine sections, embedded in paraffin and stained with hematoxylin and eosin, were used in checking pathologic changes.

The scarlet red preparations were examined microscopically, using both direct and polarized light.

15. Bell, E. T.: Am. J. Path. **14**:691, 1938.

In two series of cases, selected on the basis of the presence or the absence of demonstrable anisotropic lipoid deposited in tubular epithelium, sections were cut from the routine paraffin blocks and stained in such a way as to facilitate the detection of changes in glomerular structure, Mallory's aniline blue stain[16] being employed.

ANALYSIS AND COMMENT

Four hundred and thirty cases were analyzed as to cause of death, lesions of the kidneys, age, hours post mortem and the amount, distribution and refractile qualities of stained lipoids in the kidneys.

TABLE 1.—*Hours Post Mortem in Relation to Amount of Stainable Lipoid*

Hours Post Mortem	Cases	Number Without Stainable Lipoid	Number With Stainable Lipoid	Number with Given Amount of Stainable Lipoid		
				Slight	Moderate	Marked
Less than 5	100	13	87	42	36	9
5 to 11.9	130	31	99	63	24	12
12 to 23.9	141	42	99	62	24	13
More than 24	59	14	45	24	16	5
Total	430	100	330	191	100	39

TABLE 2.—*Age in Relation to Amount of Stainable Lipoid*

Age Decade	Cases	Number Without Stainable Lipoid	Number With Stainable Lipoid	Number with Given Amount of Stainable Lipoid		
				Slight	Moderate	Marked
First	34	19	15	11	3	1
Second	12	8	4	3	0	1
Third	35	8	17	17	7	3
Fourth	39	12	27	10	11	6
Fifth	56	13	43	22	14	7
Sixth	88	16	72	43	21	8
Seventh	81	8	73	46	21	6
Eighth	66	12	54	30	19	5
Ninth	18	4	14	9	4	1
Tenth	1	1	0	0	0	1
Total	430	100	330	191	100	39

In table 1 it is evident that the number of hours post mortem does not affect the amount of stainable lipoid in the kidney. The average number of hours post mortem for the 39 cases showing marked deposition of stainable lipoid was slightly less than twelve; for the 100 cases presenting no stainable lipoid, the average was slightly more than thirteen.

In table 2 the 430 cases were tabulated as to age in decades and as to amounts of stainable lipoid. The ages of the subjects included in this series varied from 1 day to 90 years. Except as is shown in the first two decades, no significant variations were detected. Of the 34 persons less than 10 years of age, 11 were less than 1 year old. In the cases of

16. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938, p. 153.

2 of these 11 children small quantities were seen in the ascending loops of Henle; in the cases of 8 none was stained. It appears that, except possibly in infancy and early childhood, age cannot be directly related to the quantity of stainable lipoid in the kidney.

Table 3 shows no direct relation between amounts of stainable lipoid in the kidney and causes of death other than disease of the kidney.

Data as to the incidence, quantity and distribution of isotropic and anisotropic lipoid in relation to renal lesions are compiled in tables 4, 5, 6, 7 and 8.

The largest total amounts of stainable lipoid include deposits of lipoid other than in the tubular epithelium; this was especially to be noted in diffuse glomerulonephritis. Also to be explained on the basis of fre-

TABLE 3.—*Causes of Death in Relation to Amounts of Stainable Lipoid*

Cause of Death	Cases	Number Without Stainable Lipoid	Number With Stainable Lipoid	Number with Given Amount of Stainable Lipoid		
				Slight	Moderate	Marked
Lobar pneumonia	25	8	17	7	5	5
Lobular pneumonia	92	20	72	40	25	7
Other acute infections	50	24	25	22	12	1
Tuberculosis	45	13	32	15	14	3
Syphilis	12	2	10	10	0	0
Diffuse glomerular nephritis	9	0	9	3	2	4
Arterial and arteriolar atherosclerosis						
Renal	7	0	7	3	2	2
Extrarenal	52	5	47	33	11	3
Traumatic injury	20	5	15	13	2	0
Malignant neoplasia	39	5	34	16	15	3
Exogenous poisons	4	1	3	2	0	1
Miscellaneous	58	13	45	26	10	9
Undetermined	8	4	4	1	2	1
Total	430	100	330	191	100	39

quent occurrence of lipoid deposits in other sites as well as in the tubular epithelium is the relatively high incidence of stainable lipoid in chronic inflammatory lesions (chronic glomerulonephritis and chronic diffuse glomerulonephritis) and in vascular nephrosclerosis.

In the tubular epithelium of the kidney the incidence, quantity and distribution of isotropic lipoid did not vary significantly with the renal lesions. Isotropic lipoid was more frequently deposited in the epithelium lining the ascending loops of Henle than in that lining the convoluted tubules; moreover, when there were deposits of lipoid at both sites, the heavier concentration more frequently appeared in the former situation. Stainable lipoid was generally patchily distributed in the epithelium lining the convoluted tubules and more diffusely deposited in the epithelium lining the ascending loops of Henle. Although deposits of anisotropic lipoid were noted in the tubular epithelium in 13 per cent of the 430 cases studied, the incidence of this change appeared to vary in

TABLE 4.—*Renal Lesions in Relation to Incidence and to Amounts of Stainable Isotropic and Anisotropic Lipoid, Without Regard to Distribution*

Renal Lesion	Cases	Isotropic Lipoid					Anisotropic Lipoid				
		Number Without Lipoid	Number With Lipoid	Number with Given Amount			Number Without Lipoid	Number With Lipoid	Number with Given Amount		
				Slight	Moderate	Marked			Slight	Moderate	Marked
Nephrosis (nonchemical)	73	25	48	23	16	9	70	3	1	1	1
Mercury nephrosis	3	1	2	2	0	0	3	0	0	0	0
Amyloidosis	2	0	2	0	0	2	0	2	1	1	0
Glomerulonephritis	16	2	14	5	4	5	7	9	4	3	2
Pyemic nephritis	5	2	3	1	1	1	4	1	0	1	0
Pyelonephritis	25	6	19	15	2	2	19	6	6	0	0
Tuberculosis	9	1	8	3	4	1	9	0	0	0	0
Chronic focal nephritis	48	14	34	22	10	2	42	6	6	0	0
Vascular nephrosclerosis	172	20	152	94	46	12	106	66	53	13	0
Miscellaneous	21	7	14	8	6	0	17	4	2	2	0
No lesions recognized (excluding "membranous" change)	56	22	34	18	11	5	48	8	5	3	0
Total	430	100	330	101	100	39	325	105	78	24	3

TABLE 5.—*Renal Lesions in Relation to Distribution and Amount of Isotropic Lipoid in the Tubular Epithelium*

Renal Lesion	Cases	Number Without Lipoid	Number With Lipoid	Number with Given Distribution				Number with Given Amount					
				Convoluted Tubules Only	Both		Henle's Ascending Loop Only	Convoluted Tubules			Ascending Loop of Henle		
					C > H	H > C		Slight	Moderate	Marked	Slight	Moderate	Marked
Nephrosis (nonchemical)..	73	30	43	4	8	21	10	13	19	1	10	19	10
Mercury nephrosis.....	3	1	2	0	1	1	0	2	0	0	1	1	0
Amyloidosis.....	2	0	2	0	0	2	0	0	2	0	0	1	1
Glomerulonephritis.....	16	4	12	3	5	4	0	2	8	2	2	5	2
Pyemic nephritis.....	5	2	3	0	0	2	1	1	1	0	1	1	1
Pyelonephritis.....	25	12	13	1	6	4	2	6	5	0	6	4	2
Tuberculosis.....	9	1	8	0	3	2	3	1	4	0	2	5	1
Chronic focal nephritis....	48	18	30	3	4	15	8	12	10	0	15	6	6
Vascular nephrosclerosis..	172	58	114	16	29	41	28	41	38	7	31	51	16
Miscellaneous.....	21	9	12	2	3	4	3	6	3	0	4	5	1
No lesions recognized (excluding "membranous" change).....	56	26	30	0	2	17	11	6	11	2	8	16	6
Total.....	430	161	269	29	61	113	66	90	101	12	80	114	46
				90		179		203			240		

TABLE 6.—*Renal Lesions in Relation to Distribution and Amount of Anisotropic Lipoid in the Tubular Epithelium*

Renal Lesion	Cases	Number Without Lipoid	Number With Lipoid	Number with Given Distribution				Number with Given Amount					
				Convoluted Tubules Only	Both		Henle's Ascending Loop Only	Convoluted Tubules			Ascending Loop of Henle		
					C > H	H > C		Slight	Moderate	Marked	Slight	Moderate	Marked
Nephrosis (nonchemical)..	73	70	3	0	0	1	2	0	1	1	2	0	1
Mercury nephrosis.....	3	3	0	0	0	0	0	0	0	0	0	0	0
Amyloidosis.....	2	0	2	0	1	0	1	0	1	0	2	0	0
Glomerulonephritis.....	16	7	9	4	0	5	0	4	3	2	0	3	2
Pyemic nephritis.....	5	4	1	0	0	1	0	0	1	0	0	1	0
Pyelonephritis.....	25	20	5	1	0	0	4	1	0	0	4	0	0
Tuberculosis.....	9	9	0	0	0	0	0	0	0	0	0	0	0
Chronic focal nephritis....	48	45	3	2	0	0	1	2	0	0	1	0	0
Vascular nephrosclerosis..	172	126	46	14	5	10	17	20	10	0	25	7	0
Miscellaneous.....	21	17	4	3	0	0	1	2	1	0	0	2	0
No lesions recognized (excluding "membranous" change).....	56	50	6	1	2	3	0	3	3	0	3	2	0
Total.....	430	351	79	25	8	20	26	32	20	3	37	15	3
				33		46		55			55		

TABLE 7.—*Renal Lesions in Relation to Deposition of Stainable Lipoid, Isotropic and Anisotropic, in the Walls of Blood Vessels and in Interstitial Tissues*

Renal Lesion	Total Number of Cases	Isotropic Lipoid					Anisotropic Lipoid				
		In Blood Vessels				In Interstitial Tissues, Cases	In Blood Vessels				In Interstitial Tissues, Cases
			Number with Given Distribution					Number with Given Distribution			
		Cases	Arteries	Arterioles	Glomeruli		Cases	Arteries	Arterioles	Glomeruli	
Nephrosis (nonchemical)	73	25	3	22	3	3	0	0	0	0	0
Mercury nephrosis	3	2	0	2	0	0	0	0	0	0	0
Amyloidosis	2	2	0	2	2	2	1	0	1	0	2
Glomerulonephritis	16	10	1	10	7	4	6	2	3	5	3
Pyemic nephritis	5	0	0	0	0	1	0	0	0	0	0
Pyelonephritis	25	10	2	10	4	7	2	0	2	0	2
Tuberculosis	9	2	0	1	2	0	0	0	0	0	0
Chronic focal nephritis	48	14	3	14	4	6	1	0	1	0	1
Vascular nephrosclerosis	172	118	16	114	32	17	39	5	35	7	4
Miscellaneous	21	5	0	3	2	2	0	0	0	0	0
No lesions recognized (excluding "membranous" change)	56	12	3	8	1	3	2	0	1	1	0
Total	430	200	28	186	57	45	51	7	43	13	12

TABLE 8.—*Distribution of Stainable Lipoid, Isotropic and Anisotropic, in the Subclasses of Glomerulonephritis and Vascular Nephroclerosis*

	Variety of Lesion	Total Number of Cases	Isotropic Lipoid						Anisotropic Lipoid					
			Cases with Lipoid	Number with Given Distribution				In Interstitial Tissues	Cases with Lipoid	Number with Given Distribution				In Interstitial Tissues
				Tubules	Arteries	Arterioles	Glomeruli			Tubules	Arteries	Arterioles	Glomeruli	
Glomerulonephritis	Acute diffuse	2	1	1	0	1	0	0	0	0	0	0	0	0
	Subacute diffuse	5	4	4	0	3	2	2	4	4	0	1	1	1
	Chronic diffuse	6	6	6	1	5	4	1	4	4	2	2	3	1
	Focal embolic	3	3	1	0	1	1	1	1	1	0	0	1	1
Total		16	14	12	1	10	7	4	9	9	2	3	5	3
Vascular nephrosclerosis	Accelerated arteriolonephrosclerosis	1	1	1	1	1	1	0	1	1	0	1	1	0
	"Benign" arteriolonephrosclerosis	39	36	24	4	34	18	8	23	17	3	16	5	2
	Arterionephrosclerosis	132	115	89	11	79	13	9	42	28	2	18	1	2
Total		172	152	114	16	114	32	17	66	46	5	35	7	4

direct relation to the extent and degree of glomerular injury; the highest incidence was shown in diffuse glomerulonephritis and in arteriolonephrosclerosis. Anisotropic lipoid was ordinarily deposited in heavier concentration in the epithelium lining the ascending loops of Henle than in that lining the convoluted tubules; however, it did not appear in the one site more frequently than in the other.

In the order of incidence of such change in the renal vascular structures, those which most frequently presented deposits of stainable lipoid were arterioles, glomeruli and arteries. The highest incidence of deposits of isotropic and of deposits of anisotropic lipoid in the walls of arteries and arterioles occurred in chronic diffuse glomerulonephritis and in arteriolonephrosclerosis. In these two varieties of Bright's disease the rates of incidence of lipoid deposition in arteries and in arterioles were almost identical. In general, the amount of lipoid deposited in the walls of arteries and arterioles, and the incidence of this change, varied directly with the degree and the incidence of arteriosclerosis and arteriolosclerosis. Although deposits of stainable lipoid were less frequently noted in the walls of arteries than in those of arterioles, in arteries the lipoid more frequently was seen in atheromatous plaques. Arteriolosclerosis of the kidney, without regard to its degree and to whether it was primarily or secondarily related to parenchymal lesions, was characterized by the appearance, in localized foci, of lipoid deposited in the thickened intimal coats of the blood vessels.

As to the glomeruli, a decidedly higher incidence of stainable lipoid occurred in chronic diffuse glomerulonephritis than in any other lesion. In chronic diffuse glomerulonephritis, lipoid deposited in the glomeruli was more frequently in part anisotropic than in any other lesion. Deposits of stainable lipoid were noted to occur frequently in the glomeruli in arteriolonephrosclerosis but to be only occasionally in part anisotropic.

Deposits of stainable lipoid, occasionally in part anisotropic, appeared inconstantly in the interstitial tissues related to localized areas of tubular degeneration and of interstitial scarring. Such deposits of lipoid in the interstitial tissues occurred most frequently in diffuse glomerulonephritis and in chronic pyelonephritis but were also occasionally noted in vascular nephrosclerosis and in chronic focal nephritis of undetermined genesis.

Tables 9 and 10 show the results of a comparative study of 24 cases presenting anisotropic lipoid in considerable amount deposited in the tubular epithelium and of 24 cases in which no such change could be detected. Sections of kidney from each case were stained with Mallory's aniline blue to facilitate detection of changes in glomerular structure. It is to be noted that whereas some degree of thickening of the basement membrane could be detected in 12 of the 24 cases of the control series, it

TABLE 9.—*Thickening of the Glomerular Capillary Basement Membrane in Twenty-Four Cases Presenting Largest Amounts of Anisotropic Lipoid in the Tubular Epithelium*

Case No.	Age	Hours Post Mortem	Cause of Death	Renal Lesion (Other Than "Membranous")	Thickening of Membrane
1	29	1.5	Undetermined.....	Nephrosis.....	Slight
2	28	3.5	.....	.....	Slight
3	54	3.0	.....	Acute diffuse interstitial nephritis	Slight
4	59	7.0	Lobular pneumonia.....	Subacute diffuse glomerulonephritis	Slight
5	44	3.0	Glomerulonephritis.....	.....	Slight
6	68	19.0	.....	Chronic diffuse glomerulonephritis	Slight
7	61	10.0	.....	.....	Slight
8	56	15.0	.....	.....	Moderate
9	72	4.0	.....	.....	Marked
10	42	14.0	Pyemia.....	Pyemic nephritis.....	Slight
11	38	5.0	Accelerated arteriolonephrosclerosis	Accelerated arteriolonephrosclerosis	Slight
12	38	13.0	Arteriolonephrosclerosis	Arteriolonephrosclerosis	Slight
13	46	16.0	.....	.....	Slight
14	55	15.0	Rupture of syphilitic aortic aneurysm	.....	Slight
15	55	10.0	Lobular pneumonia.....	.....	Slight
16	59	16.0	Pulmonary infarction...	Arterionephrosclerosis...	Slight
17	69	1.5	.....	.....	Slight
18	76	12.0	Lobular pneumonia.....	.....	Slight
19	63	120.0	.....	.....	Slight
20	42	36.0	Diabetes mellitus.....	Glycogenic infiltrate.....	Slight
21	49	16.0	.....	No lesions recognized....	Slight
22	1.5	19.0	Impetigo.....	.....	None
23	90	34.0	Lobular pneumonia.....	.....	Slight
24	0.5	6.5	Mastoiditis (pulmonary abscess)	.....	None

TABLE 10.—*Thickening of the Glomerular Capillary Basement Membrane in Twenty-Four Cases Without Detectable Amounts of Anisotropic Lipoid in the Tubular Epithelium*

Case No.	Age	Hours Post Mortem	Cause of Death	Renal Lesion (Other Than "Membranous")	Thickening of Membrane
1	22	5.0	Pulmonary tuberculosis	Nephrosis.....	Slight
2	35	1.5	Rheumatic carditis; lobular pneumonia	.....	None
3	58	2.5	Lobar pneumonia.....	.....	None
4	45	6.0	Pulmonary tuberculosis	Acute diffuse glomerulonephritis	None
5	30	12.0	Subacute bacterial endocarditis	Subacute diffuse glomerulonephritis	None
6	38	12.0	.....	.....	Slight
7	41	2.5	Glomerulonephritis.....	Chronic diffuse glomerulonephritis	Marked
8	22	7.0	.....	.....	Slight
9	25	2.0	Acute bacterial endocarditis	Embolic glomerulonephritis	None
10	51	11.0	Pyemia.....	Pyemic nephritis.....	None
11	71	6.0	Pyelonephritis.....	Pyelonephritis.....	Slight
12	71	4.0	.....	.....	None
13	71	13.0	General arteriosclerosis; coronary sclerosis	Arteriolonephrosclerosis	Slight
14	73	4.0	.....	.....	None
15	70	7.0	Cerebral infarction.....	.....	Slight
16	82	5.0	Carcinoma.....	.....	None
17	35	11.0	Lobular pneumonia.....	.....	Slight
18	86	2.5	.....	Arterionephrosclerosis...	Slight
19	78	3.5	.....	.....	Slight
20	71	4.0	Coronary sclerosis.....	.....	Slight
21	57	3.0	Traumatic hemorrhage..	.....	None
22	34	24.0	Syphilitic aortitis and aortic valvulitis	Glycogenic infiltrate.....	None
23	13	2.5	Undetermined.....	No lesions recognized....	None
24	44	4.0	Intestinal obstruction...	.....	Slight

appeared in 22 of the 24 cases in which anisotropic lipoid was deposited in the tubular epithelium. In the latter series the 2 cases in which a membranous change could not be detected were those of children, respectively 0.5 and 1.5 years old. In none of the cases of this series was a diagnosis of "lipoid nephrosis" made clinically, nor does a review of the clinical records indicate that this diagnosis might in any case have been justified from the point of view that "lipoid nephrosis" is a specific disease entity.

There appears to be significant association of disease of the glomerular tufts with deposition of anisotropic lipoid in the tubular epithelium.

SUMMARY

A series of kidneys obtained routinely at necropsies and representing various pathologic changes were studied as to the incidence, quantity, distribution and refractility of stainable lipoids. The method used for the staining of lipoids in the kidneys was Herxheimer's alkaline alcoholic scarlet red on frozen sections of formaldehyde-fixed tissues. The scarlet red preparations were examined microscopically under both direct and polarized light.

In the present series no apparent relation exists between age of patient, hours post mortem and causes of death (other than renal disease), on the one hand, and incidence, quantity and distribution of stainable lipoid, on the other.

Stainable lipoid of interstitial distribution tends to be deposited in areas of scarring—the sequelae of old inflammatory lesions or of vascular nephrosclerosis. It is occasionally in part anisotropic.

The amount of lipoid deposited in arterial and arteriolar walls and the incidence of this change vary directly with the degree and the incidence of arteriosclerosis and arteriolosclerosis. Arteriolosclerosis of the kidney, without regard to whether it is primarily or secondarily related to parenchymal lesions, is essentially atherosclerosis.

Stainable lipoid is rather commonly deposited in scarred glomeruli without regard to the genesis of the glomerular lesion but has its highest incidence, and is most frequently in part anisotropic, in diffuse glomerulonephritis.

In kidneys obtained routinely at necropsies isotropic lipoid is commonly present in moderate amounts in the epithelium of the convoluted tubules but occurs more frequently and in slightly heavier concentration in the epithelium lining the ascending loops of Henle. The lipoid of the convoluted tubules tends to be patchy in distribution, while that in Henle's loops is ordinarily more diffusely distributed. About 13 per cent of such kidneys are found to have deposits of anisotropic lipoid in the

tubular epithelium. The highest incidence of such deposits is associated with those conditions in which the glomeruli present evidence of inflammatory or degenerative changes, often leading to appreciable thickening of the glomerular capillary basement membrane. Anisotropic lipoid tends to accumulate in slightly heavier concentration in the epithelium lining the ascending loops of Henle than in the convoluted tubules.

It appears that the demonstration of deposits of anisotropic lipoid in the renal tubular epithelium, with or without associated membranous changes in the glomerular structure, does not justify the histologic diagnosis of "lipoid nephrosis" in the sense that this condition is a disease entity.

PATHOLOGY OF DISSEMINATED LUPUS ERYTHEMATOSUS

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INTRODUCTION

After Hebra's [1] original description of lupus erythematosus it was regarded as a unique, but in its effect not particularly serious, local skin disease. While later reports by Cazenave [2] and others indicated that this chronic alteration of the skin may become very intense, it seemed established that the malady remained localized to the skin. In 1872, however, Kaposi [3] reported observations which demonstrated that "lupus erythematosus may also appear as a disseminated or generalized acute or subacute febrile eruption and that in such circumstances intense local and constitutional symptoms may affect the organism and may even endanger or destroy the life of the patient." He recognized that females are more frequently affected by the acute form than males. While he was inclined to believe that the primary cutaneous efflorescence was identical in the chronic and acute types, he nevertheless recognized a fundamental difference in the morbid process as it affects the whole organism. For a long time dermatologists disagreed as to the existence and identity of this acute form of lupus erythematosus.

At the beginning of the century Jadassohn [4] summarized contemporary dermatologic experience in the recognition of acute lupus erythematosus as a constitutional disease and called attention to certain organic manifestations. He mentioned joint symptoms, ulceration of mucous membranes, glandular swelling and particularly renal involvement. These manifestations could be due, he thought, only to a "flooding of the organism with infectious or toxic material." The enunciation by

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1. Hebra, F.: Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien **1**:40, 1845.
2. Cazenave, A.: Ann. d. mal. de la peau **3**:297, 1851.
3. Kaposi, M.: Arch. f. Dermat. u. Syph. **4**:36, 1872.
4. Jadassohn, J.: Lupus erythematodes, in Mracek, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1904, vol. 3.

Boeck [5] that the disease was of tuberculous origin dominated the literature of this period and later. The futility and fallacy of this belief have been adequately treated by Keil.[6]

More recently the systemic implications of acute lupus erythematosus have received much more consideration than the dermatologic aspects (Goeckerman [7]; Mook, Weiss and Bromberg [8]; Baehr [9]; Baehr, Klemperer and Schifrin [10]; Baehr [11]; Montgomery [12]).

Autopsy reports on acute lupus erythematosus were first presented by Kaposi.[3] They were in no way significant, and death was attributed to intercurrent pneumonia in some of the cases and to tuberculosis in others. In the following fifty years there was a considerable number of necropsies on persons dying with this disease. It is amazing that the postmortem studies during this period disclosed nothing unusual, and it is more amazing that clinicians and pathologists for so many years seem to have been satisfied that so striking a clinical picture should not be associated with some more unusual pathologic alterations at necropsy than tuberculosis and pneumonia. The reason for this complacency may have been a peculiarly narrow preoccupation with the problem of etiology; indeed, it is strange to see that all the anatomic investigations of these years seem to have exhausted themselves in the answer to one question: Is acute lupus erythematosus due to tuberculosis or not? With a startling lack of critique, the proponents of the affirmative accepted every vestige of a tuberculous infection as proof for their theory and completely disregarded the most plausible explanation that the wasting disease might have been responsible for an acute exacerbation of tuberculosis whenever this was encountered. The opposition, on the other hand, almost triumphantly pointed to every instance in which autopsy had failed to disclose a tuberculous focus, but did not make any new contribution. This impasse was first breached by the observations of Libman and Sacks.[13] While the title of their article does not refer to

5. Boeck, C.: Arch. f. Dermat. u. Syph. **42**:71, 1898.

6. Keil, H.: Arch. Dermat. & Syph. **28**:765, 1933.

7. Goeckerman, W. H.: J. A. M. A. **80**:542, 1923.

8. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Arch. Dermat. & Syph. **24**:786, 1931.

9. Baehr, G.: Tr. A. Am. Physicians **46**:87, 1931.

10. Baehr, G.; Klemperer, P., and Schifrin, A.: Tr. A. Am. Physicians **50**: 139, 1935.

11. Baehr, G.: Disseminated Lupus Erythematosus, in Cecil, R. L.: A Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, p. 523.

12. Montgomery, H.: Disseminated Lupus Erythematosus as a Systemic Disease, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1936, vol. 4, pt. 1, chap. 1-C, p. 44.

13. Libman, E., and Sacks, B.: Arch. Int. Med. **33**:701, 1924.

the subject, their report represents the first significant contribution to the morbid anatomy of acute lupus erythematosus.

Although cutaneous manifestations were present in only 2 of their 4 cases, they pointed out that "the occurrence of an eruption on the face and elsewhere resembling acute lupus erythematosus disseminatus is important if only to attract attention to the possible existence of the atypical form of endocarditis." This association became more evident in the report of Gross,[14] who found concomitant lupus erythematosus and atypical verrucous endocarditis in 5 of his 11 cases of the latter.

Baehr, Klemperer and Schifrin,[10] in a more comprehensive study, found acute lupus erythematosus in association not only with endocardial lesions but more characteristically with certain well defined alterations in the blood vessels, especially those of the kidney.

The significance of such systemic vascular alterations in association with acute lupus erythematosus was subsequently stressed also by Jarcho,[15] Ginzler [16] and Denzer and Blumenthal.[17]

Since the publication of the article by Baehr, Klemperer and Schifrin in 1935, we have had the opportunity of studying 12 additional cases of acute lupus erythematosus. This new material disclosed certain alterations which had not been recognized in the older material. The older material, especially the hearts, was therefore restudied. This recent investigation seems to throw new light on a fundamental tissue damage in acute lupus erythematosus which is basically responsible for the vascular, the endocardial, the renal and other alterations in this disease.

ANALYSIS OF CASES

We have had in our autopsy material 35 cases of disseminated lupus erythematosus. All have been carefully studied. However, in making a statistical pathologic analysis, we have drawn only from the most recent consecutive 20 cases, since these presented the most complete set of tissues available for examination. Abstracts of these 20 cases are appended to this report. There were no significant pathologic (or, for that matter, clinical) findings in the first 15 cases not also present in the last 20, and vice versa. Any statistical survey of the incidence of various visceral lesions has certainly greater significance if made on a small number of complete cases than if made on a large number of incomplete ones.

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14. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 527.

15. Jarcho, S.: Bull. Johns Hopkins Hosp. **59**:262, 1936.

16. Ginzler, J. M., and Fox, T. T.: Arch. Int. Med. **65**:26, 1940.

17. Denzer, B. S., and Blumenthal, S.: Am. J. Dis. Child. **53**:525, 1937.

Serous Membranes.—Pericarditis occurs frequently. It reaches its maximal development in universal fibrous adhesion of the visceral and parietal layers of the pericardium, with obliteration of the sac. The conglutinating tissue often has a strikingly thick, gelatinous, succulent appearance. The process may extend beyond the limits of the sac with the production of similar adhesions between the parietal layer of the pericardium and the pleura. Less extensive involvement results in focal adhesive bands.

Diffuse or focal fibrinous pericarditis is frequent. Nevertheless, undue emphasis ought not to be placed here, since this finding cannot be dissociated from the pneumonia which is so common.

In the absence of gross pericardial change, one may find histologically a striking pericardial involvement with little or no fibrinous deposit on the surface. In such cases one observes fibrosis of the adipose layer, active capillarization, fibroblast proliferation and infiltrations of plasma cells, lymphocytes, some leukocytes and large mononuclear cells. The latter have an abundant eosinophilic cytoplasm. They are consistently found in almost every pericardium in this collection of hearts, even in the absence of gross changes. The newly formed and forming capillaries are dilated and often engorged. The young connective tissue is rather loose. The fibroblasts are large. One can occasionally trace their development from actively proliferating connective tissue cells peculiar to the heart—the "myocytes" of Anitschkow (Ehrlich and Lapan [18]).

These microscopic alterations are in themselves not distinctive. There are other changes, however, which attract attention because of their unusual character.

The epicardium is essentially a loose areolar tissue reenforced by stout collagen fiber bundles. This forms a connective tissue matrix in which fat cells are embedded—the adipose layer. The superficial layer of the epicardium consists of a more compact connective tissue containing elastic as well as collagen fibers—the stratum proprium. The mesothelium covers the stratum proprium. The collagen fibers and cells in the normal loose areolar tissue of the epicardium stand out distinctly from an unstained background which is thought to consist of a very delicate mucoid ground substance difficult to demonstrate by ordinary histologic methods. This is best seen where the fat is scanty, usually adjacent to the myocardium.

Possibly the earliest epicardial changes are those seen microscopically in hearts which appear grossly normal. This is the appearance of a deeply eosinophilic substance disposed among the fibers. This substance stains red with azan and deep mahogany brown with the Bielschowsky silver stain. On casual inspection, one might dismiss this alteration as

18. Ehrlich, J. C., and Lapan, B.: Arch. Path. **28**:361, 1939.

the precipitation of a protein-rich edema fluid. It seems to differ from mere edema, however, in that it is not vacuolated and appears much more substantial than even the most dense of fluid precipitates. We are therefore more inclined to believe that we are dealing with a physicochemical alteration of the interfibrillary ground substance. This interpretation is supported by the fact that the interfibrillary alteration is associated with a striking and unequivocal change within the fibers themselves. These lose their delicate wavy appearance; they become straight and irregularly thickened. They are intensely eosinophilic and highly refractile. Their massiveness is augmented by the accretion of adherent clumps of ground substance (fig. 1 *A*).

These fiber changes have been called fibrinoid degeneration, a term first applied by Neumann.[19] We shall continue the use of this term in its purely descriptive sense. It can also, therefore, be properly applied to the altered ground substance giving the same tinctorial reactions as the altered fibers.

The alteration of fibers and ground substance is accompanied by a conspicuous proliferation of fibroblasts. Less conspicuous is the infiltration of histiocytes and leukocytes. The fibroblasts are concentrated in the foci of altered collagen fibers. The cytoplasm is often basophilic and attenuated, even fibrillar in appearance. The nuclei are pyknotic or fragmented. There is sometimes chromatolysis with suffusion of the basophilic nuclear material into the cytoplasm and intercellular ground substance.

The thick, gelatinous, adherent pericardium owes its arresting gross appearance not alone to proliferative and infiltrative tissue changes but even more to a series of alterations affecting the preexisting and the newly formed connective tissue. Here the usual sharp contrast between fibers and ground substance is obliterated. In hematoxylin-eosin preparations the fibers, cell cytoplasm and ground substance can be optically isolated under high magnification only by "stopping down" the diaphragm of the substage condenser. In the Mallory trichrome stain the ground substance assumes a pale blue homogeneous appearance, in which the deeper blue collagen fibers stand out quite clearly. The ground substance may be thought to have become "collagenized."

Not only does the ground substance become visible, but it also increases in bulk, as evidenced by splitting off of individual fibrils from large collagen bundles and wide separation of these fibrils and connective tissue cells.

Finally, fibrinoid degeneration affecting both fibers and "collagenized" ground substance is often quite conspicuous in the grossly thick, gelatinous-appearing, adherent pericardium.

19. Neumann, E.: Arch. f. mikr. Anat. **18**:130, 1880.

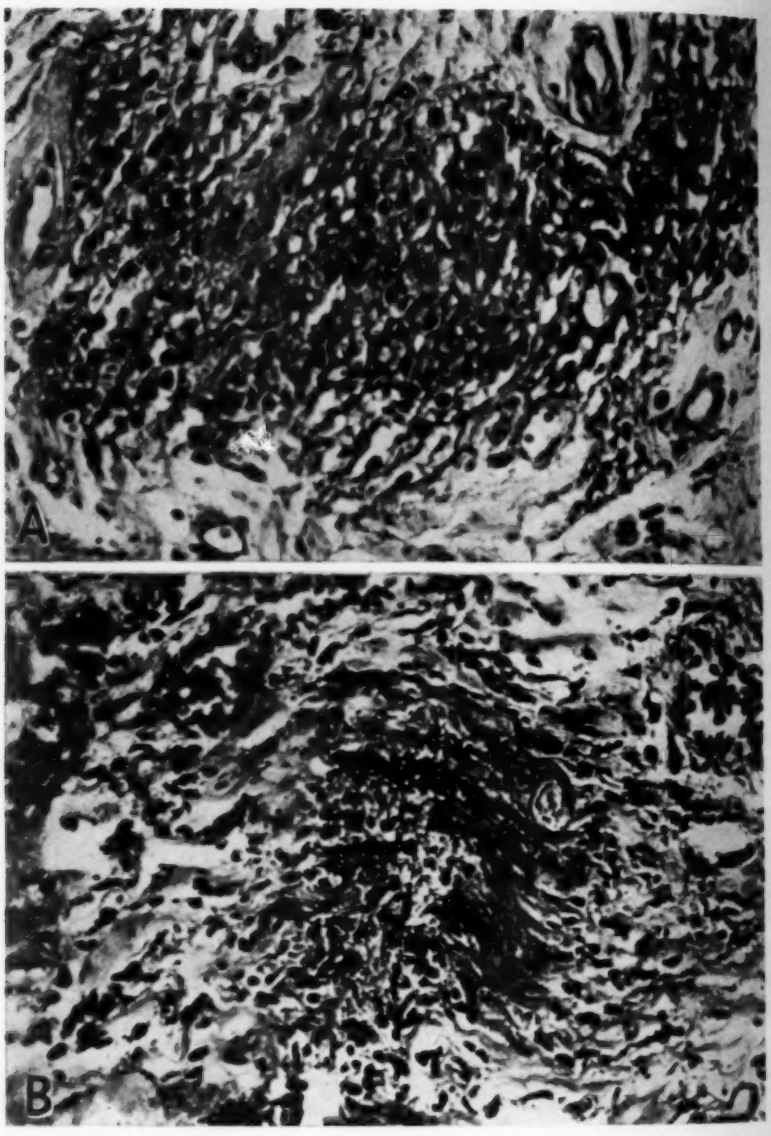

Fig. 1.—*A*, pericardium showing focal fibrinoid degeneration of collagen tissue. The continuity of the swollen, rigid and eosinophilic collagen fibers with delicate wavy normal fibers is seen at the periphery. The proliferated fibrobiasts show pyknosis and nuclear disintegration. *B*, pleura showing rigidity and swelling of collagen fibers with fragmentation. Note distortion and disintegration of fibroblastic nuclei.

Pleuritis is very frequent and more readily accounted for than pericarditis. In most cases in which it is present, pneumonia, either acute or chronic, is associated with it. Occasionally, however, it is seen together with the universally adherent pericarditis described in the foregoing paragraphs. In a few such instances the process in the pleura is grossly and microscopically identical with that found in the pericardium (fig. 1 *B*). Alteration of collagen fibers, as well as alterations of collagen within the walls of blood vessels, is found in the pleural adhesions. The vascular alterations will be described in detail later.

Very occasionally, isolated fibrous adhesions may be found in the peritoneal cavity. They are such as might be found in any abdomen and have no significance. Perisplenitis and perihepatitis, on the other hand, recur repeatedly in this series. There may be diffuse thickening of the capsules of the spleen and liver. Such thickening is fibrous and generally associated with adhesions to neighboring structures. The adhesions are independent of infarcts. Microscopically, the fibrous plaques and tags are generally well capillarized and infiltrated by large and small round cells. The nuclei of the splenic capsule sometimes assume a bizarre pyknotic appearance. The capsular fibers and the newly deposited collagenous tissue may exhibit fibrinoid degeneration as in the pericardium and pleura.

Heart.—The pericardium has already been considered under serous membranes. The most striking lesion in the heart is found in the endocardium. The endocarditis seen at the autopsy table is pathognomonic if fully developed. Such fully developed lesions, conforming to the description of Libman and Sacks,[18] were present in 6 (30 per cent) of our 20 cases. In 2 additional cases vegetations were found only on the valves and could not properly be considered pathognomonic on mere gross examination.[20]

The lesions are in general verrucous in appearance—dry granular tawny or pink vegetations varying in size from that of a pinhead to 3 or 4 mm. They may be single or conglomerate. The single lesions resemble minute beads or pyramids and are not easily removed from the endocardium. This type is more frequent on the valves. Sometimes they form large mulberry-like clusters which are actually dependent from the valvular endocardium. In a case of involvement of an auriculoventricular valve such clusters or single verrucae may extend down onto the chordae tendineae. The verrucae seen on the semilunar valves are found mostly on the ventricular surface along the lines of closure but may occur elsewhere on the same surface. Furthermore, in these same valves they are also seen on the arterial surfaces of the cusps—deep down in the sinus

20. The relationship of the vegetations in these 2 cases to those of so-called terminal thromboendocarditis is now under investigation in this laboratory.

pockets. There may be a trail of vegetations from the ventricular aspect of the semilunar valves down onto the normal endocardium of the ventricular outflow tracts. Similarly, clusters of vegetations may descend from the auricular surface of the auriculoventricular valves to the chordae tendineae and finally spread out over the apexes of the papillary muscles. A favorite localization of verrucae is in the angles between the flaps of the auriculoventricular valves and the mural endocardium. These were described by Gross and designated by him "pocket lesions." They are best discovered by turning the valve leaflet cephalad after cutting the chordae tendineae. The valvular lesions are seen grossly on both the right and the left side of the heart with equal frequency.

Mural endocardial vegetations may be small and verrucous but are most often yellowish gray, tawny or pink plaques with an irregular outline and measuring a few millimeters to as much as a centimeter in diameter. They occur nearer the base of the ventricle rather than toward the apex, i. e., in the outflow tracts or in the areas between the valve rings and the tips of the papillary muscles. Not rarely, chordae tendineae become agglutinated to subjacent mural endocardial plaques. The mural endocardial lesions are grossly and microscopically as frequent on the right as on the left side. Older mural endocardial plaques are white and fibrous.

Macroscopic endocardial vegetations were evident in 40 per cent of the cases. In an additional 20 per cent microscopic examination revealed endocardial lesions that are regarded as the early phase of the grossly visible alterations. In this initial phase, one sees focal clumps of altered ground substance in the superficial connective tissue layers of the valves, frequently just below the intact endothelium. These clumps appear as homogeneous, deeply eosinophilic masses (fig. 2 *A*). Associated with this change, but often at some distance, one finds areas of proliferation of the valvular myocytes. These exhibit a series of transformations (fig. 2 *B*) identical with those observed in the pericardium. When the clump of altered ground substance is small, the endothelium is elevated but slightly. However, with accretion of further altered ground substance, the growing mass actually protrudes beyond the limits of the surface. The endothelium may show degenerative changes, such as nuclear pyknosis and fragmentation. The protruding mass of swollen ground substance on the surface of the valve now becomes grossly evident as a verruca (fig. 3 *A*). The proliferated cellular elements already seen in the body of the valve are also found in the verruca as pyknotic, degenerated cells. It is important to note, moreover, that even within some of the larger vegetations the characteristic nuclear structure of the myocyte can occasionally still be recognized. This is proof of the intravalvular origin of the verruca. In short, the vegetations are constituted of altered valve substance and are not merely laid down on the endo-

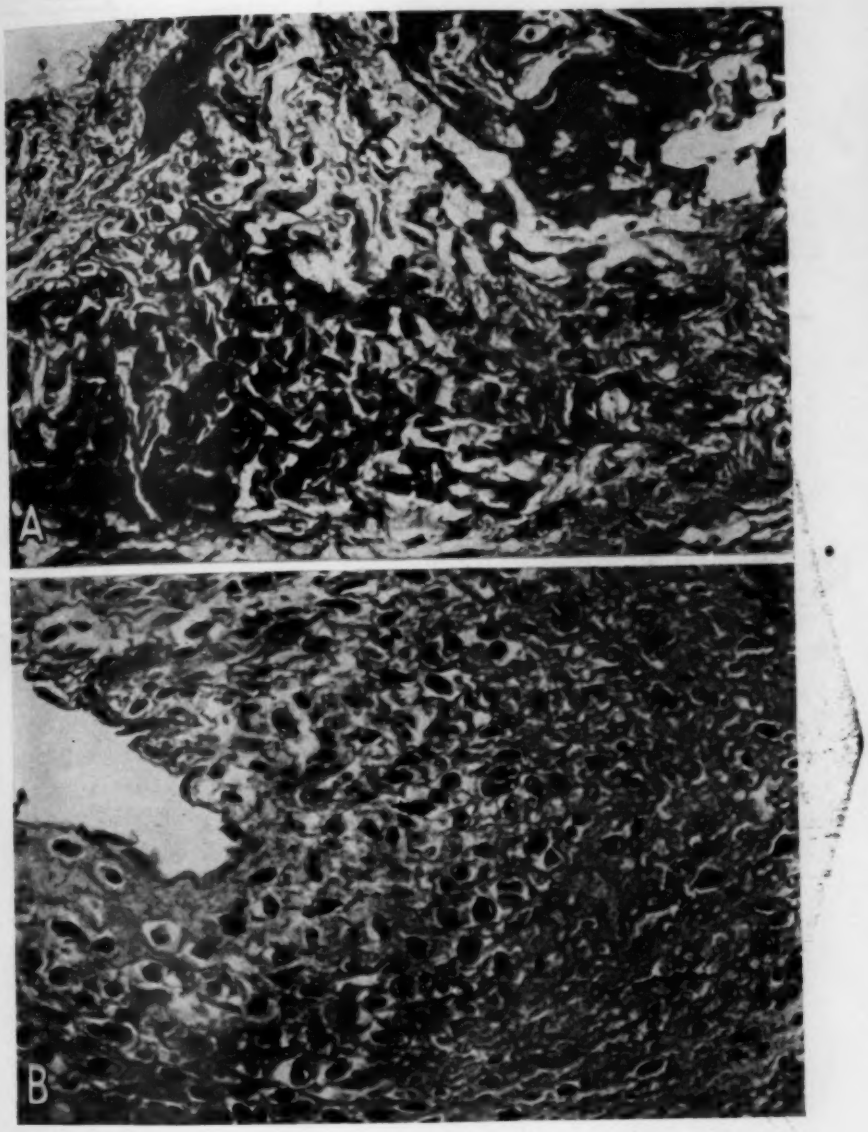

Fig. 2.—*A*, tricuspid valve showing clumps of deeply eosinophilic swollen interfibrillary ground substance. *B*, mitral valve pocket showing fibrinoid degeneration of collagen fibers and proliferation of myocytes with pyknosis and nuclear fragmentation.

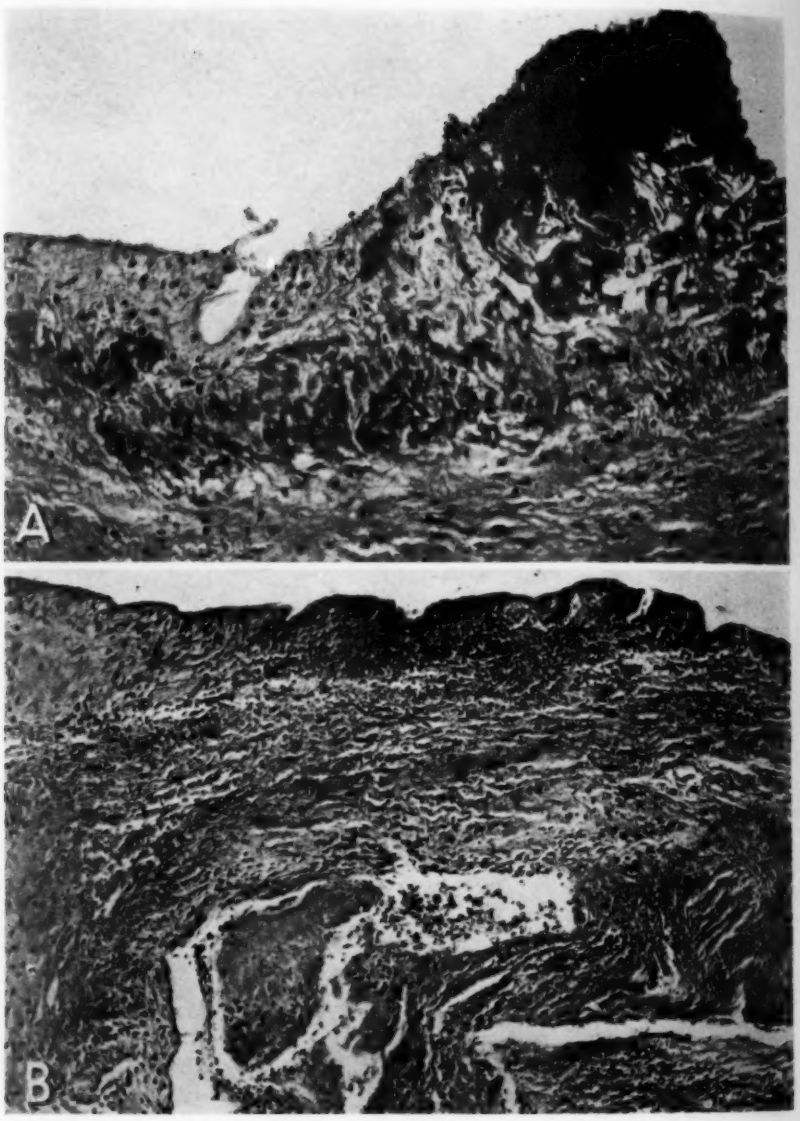

Fig. 3.—*A*, tricuspid valve. Note development of a microverruca by extrusion of swollen, altered ground substance above the surface of the valve. (The same section is seen in higher power in fig. 2 *A*.) *B*, tricuspid valve showing fibrinoid degeneration and necrosis of connective tissue throughout its entire thickness.

cardium. There is little or no accretion to the vegetation from the blood stream except in cases of superimposed bacterial endocarditis. The endocardial lesion is from the very beginning a relatively deep process. Indeed, in some cases the entire thickness of a valve leaflet participates in the reaction (fig. 3 *B*). Finally, more frequently than in rheumatic endocarditis, the ventricular aspect of the auriculoventricular valves, as well as the arterial aspect of the semilunar valves, shows endocardial lesions.

In addition to the endocardial alterations thus far described which will generally give rise to grossly visible vegetations, the collagen fibers of the deep layers of the endocardium may show conspicuous irregular thickening, homogenization and eosinophilia. As described in the pericardium, there is an associated series of cellular changes. The whole may progress to actual necrosis of the cells and fragmentation of the fibers. Such foci are conspicuous as granular basophilic masses, which on analysis consist of dustlike nuclear debris and basophilic fragments of cytoplasm and fibrils (fig. 4 *A*).

Capillarization of the lesion appears late. The capillaries invade the verruca from below and are not numerous. At the same time, fibrosis is initiated. In this stage the lesion contains a small number of capillaries, fibroblasts, lymphocytes and some plasma cells, and sometimes macrophages bearing iron pigment. The newly formed collagen tissue may in its turn suffer the same fate as the original endocardial connective tissue. And so one may find fibrinoid degeneration repeated in the newly formed fibrous tissue. The whole lesion may in this phase present the aspect of a subacute or chronic granuloma. The endocardial process may become static as a fibrous, slightly elevated plaque containing few cells. One case was noted in which such an endocardial granuloma binding the posterior papillary muscle of the left ventricle to the adjacent mural endocardium served as the site for implantation of bacteria.

The altered tissue of the endocardium in disseminated lupus erythematosus is apparently receptive to the implantation of bacteria. This occurred four times in the most recent 20 cases, i. e., four times in the 12 cases in which endocardial involvement was found either grossly or microscopically. Bacterial invasion occurs in old, not in acute, endocardial lesions. Careful search of the endocardial vegetations by culture, by examination of crushings made at the autopsy table and by examination of bacterial stains of the sectioned vegetations revealed no organisms save in the 4 cases mentioned. In 2 of these, the vegetations were large and contained many bacteria (Staphylococcus aureus in one, Streptococcus haemolyticus in the other), and there were embolic abscesses; repeated blood cultures during life were negative. In the third case a few gram-positive cocci were found in the superficial zone of one vegeta-

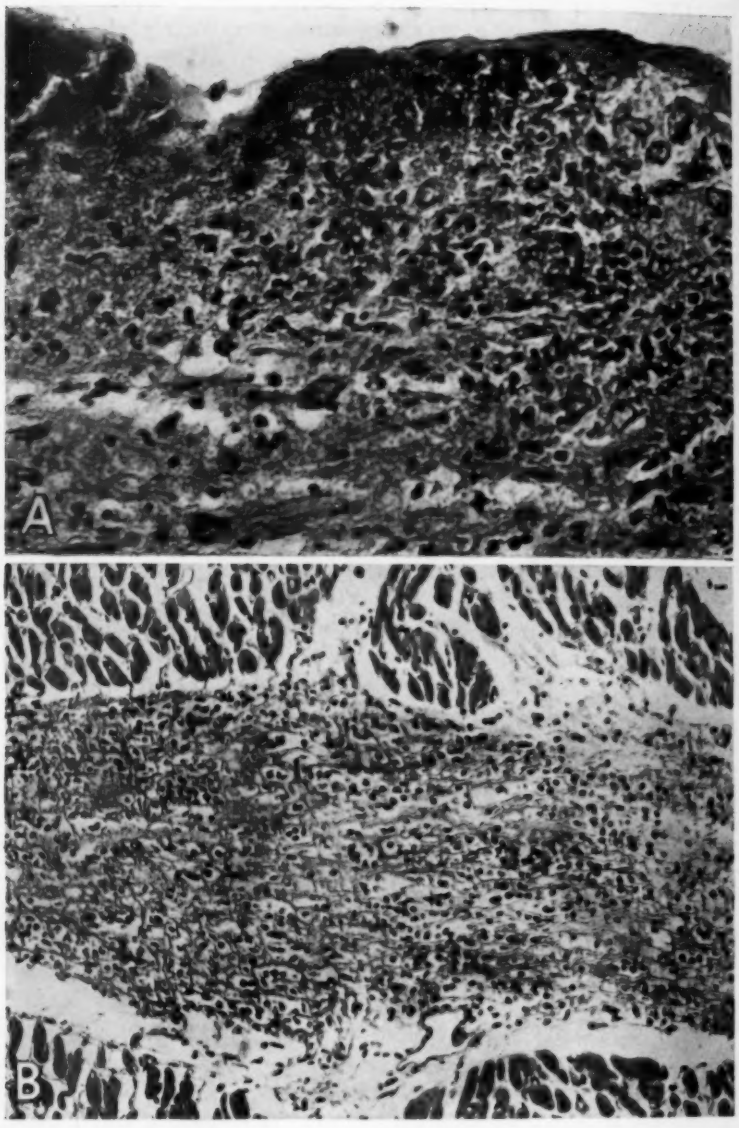

Fig. 4.—*A*, auricular surface of the mitral valve, showing necrosis and fragmentation of collagen fibers compounded with disintegrated nuclei of proliferated fibroblasts. There is a slight leukocytic infiltration. (This is a higher power magnification of the section seen in fig. 3 *B*.) *B*, intermuscular connective tissue septum of myocardium showing fibrinoid degeneration of collagen fibers with proliferation and degeneration of fibroblasts, and scattered macrophages and polymorphonuclear leukocytes.

tion; a blood culture just before death yielded Streptococcus viridans. In the fourth case one vegetation showed a few gram-positive cocci superficially; intravital blood cultures were negative. The engrafting of organisms on preexisting nonbacterial lesions must have occurred shortly before death. With some of the smaller vegetations in these 4 cases, it was not possible to decide whether the lesions may not have been bacterial from the very beginning. The presence of older lesions having the characteristic distribution and the gross and microscopic appearances of the endocarditis seen in this disease establishes the primary nonbacterial nature of the injury. Secondary bacterial engrafting on such lesions might serve as a reservoir from which other vegetations, bacterial from the beginning, may be established in other endocardial areas. It becomes important, then, to recognize the older abacterial lesions.

The alterations encountered in the myocardium may be divided into a group of "primary" changes affecting the supporting tissues and blood vessels, and secondary changes affecting the muscle fibers themselves. Changes of the connective tissue identical with those observed in the pericardium and endocardium were seen in 35 per cent of the 20 hearts subjected to statistical analysis. They were noted in the right as well as in the left ventricle. In such lesions the collagen fibers appear swollen and rigid and are deeply stained by eosin (fig. 4 *B*). There is usually an associated infiltration of lymphocytes and, less frequently, of leukocytes. The lesion is seen in those areas where connective tissue is most abundant, namely, in the neightborhood of blood vessels and in the interfascicular connective tissue planes. At the same time a conspicuous proliferation of fibroblasts is frequently observed among the altered fibers. One can occasionally trace their development from myocytes, as in the pericardium. Generally, the nuclei of the proliferated cells show distortion and pyknosis (fig. 5 *A*). The ground substance may be rendered visible as a pink-staining homogeneous matrix showing foci of basophilia. The proliferated myocytes only occasionally acquire an abundant basophilic cytoplasm. Thus, the total perivascular lesion may rarely show a superficial similarity to the Aschoff body. The definitive cellular pattern of the Aschoff body is never present however. Further, the alteration of the collagen fibers is far more conspicuous than in the Aschoff body. It must be emphasized, then, that true Aschoff bodies have not been observed in these hearts.

Fibrinoid degeneration and even necrosis are occasionally observed in the walls of small coronary arteries. These alterations are generally focal. Other vessels may contain organizing eosinophilic masses. Whether the latter are local in origin or embolic cannot be unequivocally determined. In all but a single case in which they occurred, they were associated with endocardial excrescences. One case was noted in which

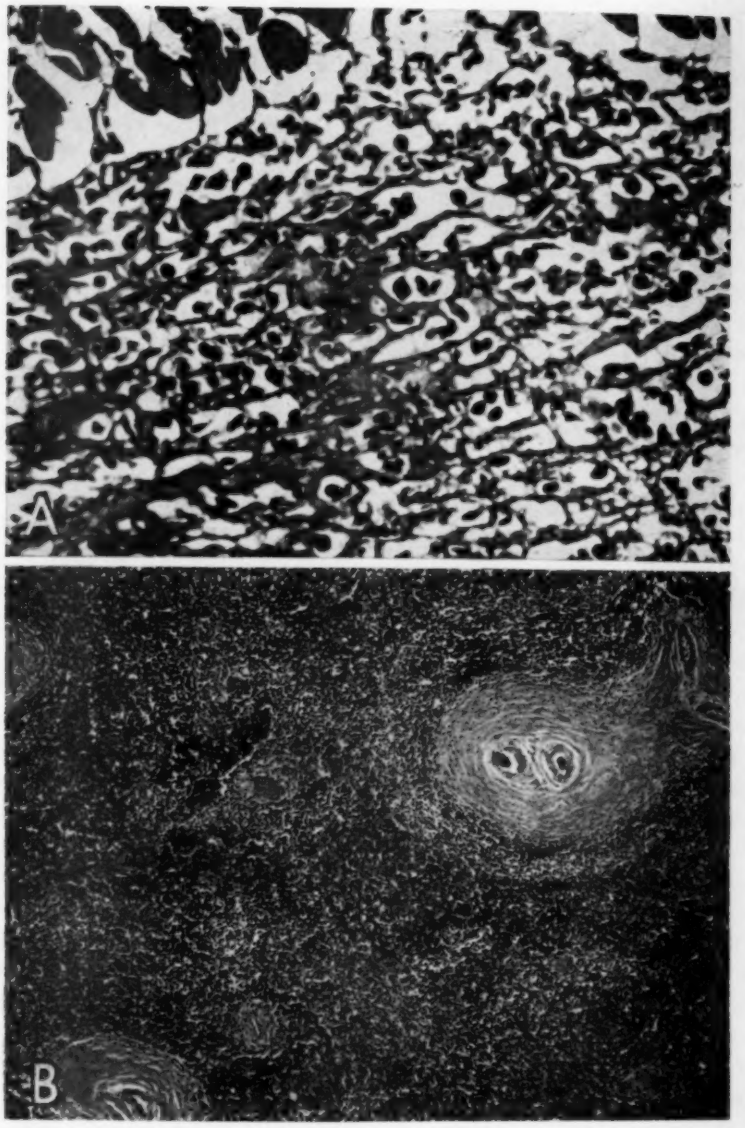

Fig. 5.—*A*, myocardium with changes the same as those seen in figure 4 *B* shown in greater magnification. *B*, spleen with thick rings of sclerotic collagen fibers around central arteries.

no such source for emboli was found, and it must be assumed that in this case, at least, they were formed locally.

Focal necrosis and atrophy of cardiac muscle fibers were found secondary to such vascular lesions. The muscle changes are therefore entirely incidental and nonspecific.

Focal acute interstitial myocarditis was seen only once. The relative frequency of such inflammation in the presence of acute infection nullifies any special significance here.

Myocardial microabscesses occurred in the single heart in which Staph. aureus was engrafted on a verrucous endocarditis.

Perivascular myocardial scars in the absence of disease of the coronary arteries could generally be linked to old rheumatic infection as evidenced by valve deformities. However, it is conceivable that perivascular myocyte proliferation with and without associated alteration of collagen may lead to such scars. This was, in fact, observed in 1 case in which the valves gave no hint of ancient rheumatic infection.

A unique change affecting the cardiac muscle fibers themselves was seen only once in the entire series. The muscle fibers were deeply eosinophilic and homogenized and contained bluish (hematoxylin) masses within the sarcoplasm. Although their form and their affinity for hematoxylin suggested calcium, von Kossa stains were negative. The alteration involves at first only part of the fiber. In this stage the muscle nuclei seem unaffected. With progressive involvement of an entire fiber, the corresponding nucleus becomes pyknotic. Finally, almost as though such fibers had become brittle, they fragment. This change occurred sporadically in small groups of fibers throughout the myocardium. Furthermore, a similar process was evident within isolated smooth muscle fibers of the coronary arteries and veins. There was no reactive inflammation and no apparent association with lesions occurring in the supporting tissue of the heart.

Lungs.—The postmortem observations do not properly reflect the remarkable clinical manifestations of pulmonary involvement in this disease—the long bouts of waxing and waning, migrating bronchopneumonia. At the time of death most of the patients exhibited bronchopneumonia of varied extent and severity. The pneumonia was in no way specific. Lobar pneumonia with a positive blood culture (Pneumococcus type XIX) occurred in a single case. Diffuse cylindric bronchiectasis and obliterating bronchiolitis were each seen once.

Lesions of systemic implication were found in the small pulmonary arteries in a single case. As elsewhere in this case, the vessels showed mural fibrinoid change, especially of the adventitia, and proliferation of adventitial cells with plasma cell infiltration.

Liver.—No single characteristic alteration was found in the series of livers examined. Nevertheless certain lesions, though relatively

infrequent, deserve mention. The capsular changes were striking and have been considered earlier.

Fibrinoid degeneration below the endothelium of sublobular and hepatic veins was seen only once. Proliferation of Kupffer cells, sometimes quite impressive, was not unusual. In a single case there was extensive focal necrosis of parenchymal cells with reactive inflammation. Such necrosis sometimes involved several lobules. In the subcapsular zone were areas of cicatrization of older lesions. Hepatic veins in the areas of necrosis often exhibited edema of their walls and parietal thrombi. Portal vein branches in this case were frequently filled with recently formed thrombi.

In 2 cases small and medium-sized hepatic arteries showed moderate to severe narrowing produced by proliferation of intimal connective tissue. Unlike the usual intimal sclerosis of arteries, in which the new tissue is laid down circularly, in these cases the newly formed fibers assumed a longitudinal arrangement and simulated in hematoxylin and eosin preparations an inner longitudinal muscle coat. We have seen this same type of intimal sclerosis of hepatic arteries in association with rheumatic heart disease. In one of the cases, the arteries showed, in addition to the intimal changes, some fibrous replacement of the media and thickening of the adventitia associated with lymphocytic infiltration.

Hepatic edema is uncommon.

Spleen.—The spleen is not particularly large. Only in 3 cases did it weigh over 300 Gm.; the largest weighed 500 Gm. Excluding the spleen of a child and an unusually small spleen, weighing only 30 Gm., the average weight of the spleens was about 260 Gm. Aside from the perisplenitis which occurred in half of the cases, the spleen had no characteristic appearance. It was as often firm as soft, possibly depending on the severity of the terminal infection. One case was noted in which the cut surface presented small grayish yellow irregular areas of necrosis. In another (Staph. aureus bacteremia) abscesses were present. Infarcts were seen in only 3 of 20 cases.

Under the microscope one lesion presented itself consistently—indeed, in 19 of the 20 cases. This is a peculiar periarterial fibrosis limited to the central and penicilliary arteries. In cross sections of these vessels the fibrosis assumes a pattern of concentric rings of stout collagen fibers, with few intercalated fibroblasts (fig. 5 *B*). The distinctive pattern clearly precludes confusion with trabeculae that bear arteries. The rings are apparently formed by slow collagenization of adventitial reticulum fibers. Further accretion of fibers is possibly established either by collagenization of preexisting periarterial argentophilic reticulum or by formation of new fibrillar reticulum which in turn undergoes collagenization. This was suggested in 2 cases by conspicuous focal reticulum cell proliferation at the periphery of sclerotic periarterial rings. The fibrous rings thus formed may attain a considerable thickness, far exceeding

the dimensions of adjacent normal trabeculae, against which they are contrasted by virtue of the onion peel arrangement of the newly formed fibers. The rings are laid down at the expense of periarterial lymphatic tissue.

We have looked for the earliest stages in the development of this lesion. The minimal lesions differ from the maximal only quantitatively. We were not able to find any consistent and unequivocal evidence of a preexisting acute injury of the arterial adventitia or periarterial reticulum which might be interpreted as the early phase of a process which culminates in a reactive periarterial fibrosis or, better, sclerosis. One case was noted in which many of the newly formed collagen fibers exhibited striking fibrinoid degeneration—eosinophilic swelling and homogenization—and even basophilia. There was associated necrobiosis of fibroblasts. The process was histologically identical with that seen, for example, in the cardiac valves, even to the deposition of clumps of homogeneous eosinophilic ground substance. One other case showed the same collagen changes within trabeculae.

Foci of necrosis were found in the red pulp in a single case. In another case there was necrosis of lymphatic tissue at the peripheries of malpighian follicles.

Kidneys.—These were generally larger and heavier than normal. The surfaces were smooth in almost every case. Occasionally, shallow stellate scars were found. In only 3 cases did the surfaces of the kidneys, particularly at the convexities, show irregularly distributed shallow red areas of atrophy contrasting with the grayish yellow normal parenchyma.[21] The majority of the kidneys showed minute petechial hemorrhages on the surface. The surfaces had no consistent color. Except for the cases in which there was gross atrophy of the parenchyma (severe vascular alteration, glomerulonephritis), the tubular system of the cortex showed little change of significance. There was occasional hyaline droplet degeneration or slight fatty infiltration of the epithelium of the convoluted tubules. The degeneration, however, was in general no more striking than what one would expect in a chronic febrile disease. The atrophic areas showed the characteristic small tubules with flattened, indifferent epithelium.

The most impressive change encountered in the kidneys is a peculiar alteration of the glomerular loops that have previously been characterized as "wire loops" because of a fancied resemblance to loops of bent wire (Baehr, Klemperer and Schifrin).[10] Such loops appear irregularly thickened and rigid, and are deeply stained by eosin (fig. 6*A*). The

21. In 3 cases not included in the series of 20 (2 were in the older series and 1 was that of a man with this disease, encountered after completion of this report), the surfaces of the kidneys were diffusely involved by this atrophic process. The appearance was reminiscent of the atrophic changes in malignant nephrosclerosis.

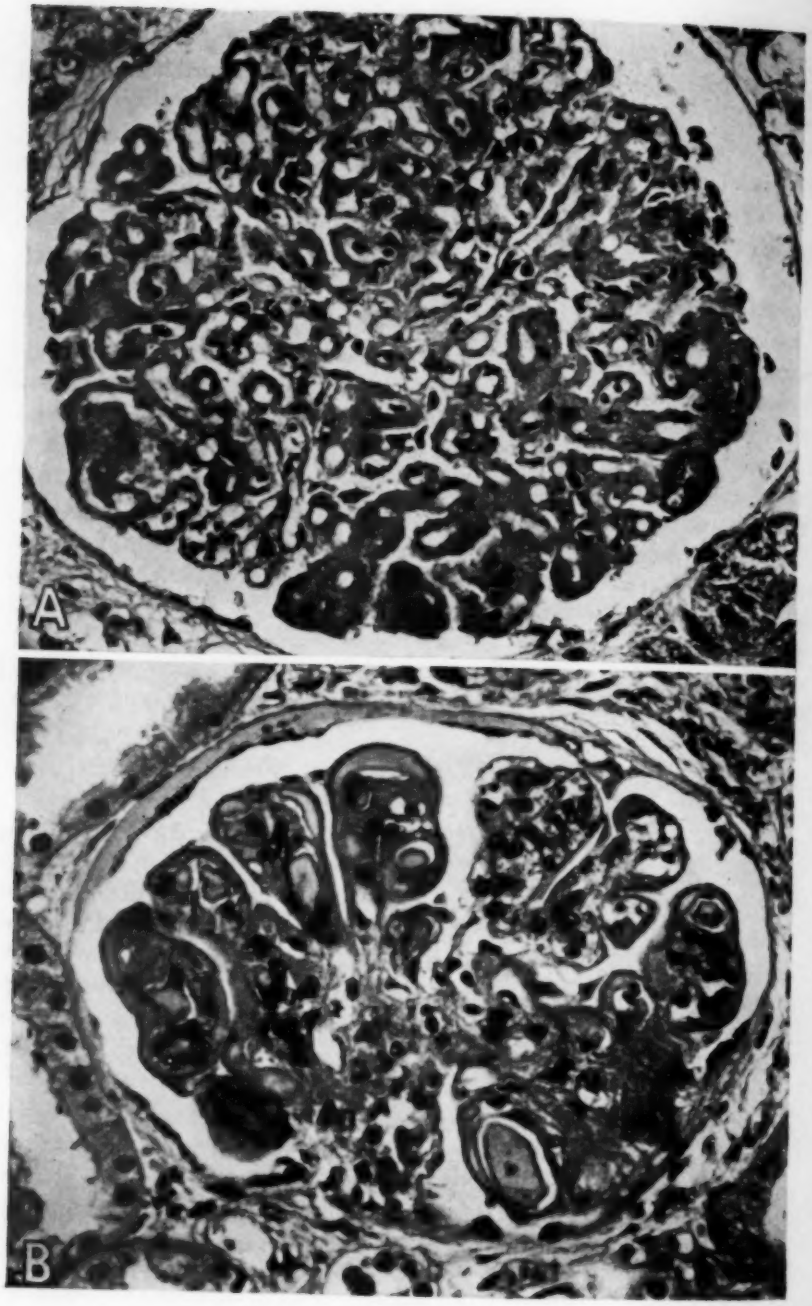

Figure 6

(See legend on opposite page)

thickening is found between the endothelium and the visceral epithelium, apparently in some relationship to the basement membrane. The appearance is similar to that of amyloid, but all stains for this substance are negative. In an unstained frozen section the rigid loops are highly refractile and glassy. Unlike the arteriosclerotic kidney, in which the thickened basement membranes of the loops stain blue, the "wire loops" in these kidneys stain pink or red with the Mallory or the azan stain. The staining is not always uniform. The basement membrane may appear as a thick pink or red loop having a discontinuous bluish core (azan). It may be entirely red or it may be more blue than red. Every loop in the glomerulus may participate in this change, or only a few of the loops. Similarly, the number of glomeruli exhibiting the change may vary from few to many. Those "wire loops" taking the red stain with azan do not give the collagen reaction with Van Gieson's or with Masson's trichrome stain. When sections are subjected to tryptic digestion, the material which gives the characteristic wire loop appearance in hematoxylin and eosin preparations is gradually dissolved out, leaving a visible space between the endothelium and the epithelium. There is apparently a graded series of changes affecting the glomerular loops. What we have just described may be looked on as a relatively bland change, possibly the result of a low grade injury. Somewheres, however, the "wire loops" have a somewhat different aspect—they stain very intensely with eosin or even acquire basophilia. The continuity of the homogeneous thickening of the loop is lost, resulting in fragmentation (fig. 6*B*). In this phase the nuclei of the focally involved glomerular loop become pyknotic and bizarre. Finally, in the most extreme type of injury the loop is found to be completely necrotic—a mass of eosinophilic and basophilic debris containing nuclear fragments. In the most severely affected loops there is a leukocytic reaction. The adjacent parietal epithelium may react by proliferation and agglutination to the necrotic loop. There is by no means a continuous series of changes in the sense that the focal necrosis of loops is the end stage of a process whose initial effect is the "wire loop." It seems rather that both the wire loop change and the focal necroses of loops are but different grades of the same alteration, which assumes one or the other

EXPLANATION OF FIGURE 6

A, glomerulus showing thickening and swelling of the basement membrane of the glomerular capillary loops.

B, glomerulus with wire loop thickening of the basement membrane. The loops are intensely eosinophilic. Some of the loops show basophilia and fragmentation leading to disintegration of the discrete loops and coalescence of the fragments (at right side of illustration).

appearance, depending on the intensity of the underlying injury. Thus, in 5 of the cases[22] necrosis of glomerular loops was present in the absence of the wire loop change (fig. 7 *A*). The latter was present in 12, while the former was present in 17 of the cases.

The capsular basement membrane occasionally exhibits an alteration apparently identical with the wire loop change in the basement membrane of the glomerulus.

In a few cases the glomerular capillaries contained "hyaline thrombi." In appearance and staining reactions these masses are similar to the substance of the glomerular "wire loops" with which they are associated (fig. 6 *B*). They probably represent an extreme development of the wire loop change in which the swollen basement membrane actually intrudes into the capillary lumen. Interpreted thus, "hyaline thrombi" becomes an erroneous designation.

Partial or complete fibrosis of glomeruli is not uncommon (fig. 7 *B*).

Stromal participation was found in 2 cases. In the first instance foci of fibrinoid degeneration and fragmentation of fibers with conspicuous fibroblast proliferation were seen. These fibroblasts in turn showed advanced necrobiosis and even necrosis. In the second case the stroma's participation was evidenced by circumscribed nodular proliferations of large fibroblasts separating and incarcerating renal tubules or bulging into veins, producing marked distortion of their lumens.

Infiltration of the stroma by lymphocytes and plasma cells was frequently encountered, but the finding carries no relevance here because of the frequency of such infiltration in a general autopsy material.

In 2 cases there was true glomerulonephritis. One, in the subacute phase, exhibited wire loop alterations in addition to the usual changes of Bright's disease. The other, in the chronic phase, showed no characteristic wire loops or loop necrosis.

The vascular lesions in the kidneys are described together with the general vascular alterations.

Lymph Nodes.—Lymph node enlargement was noted in 9 cases. In 5 of these the nodes revealed conspicuous necrosis on gross examination. Histologically, one finds irregular areas of necrosis involving the lymphatic and supporting tissue of the nodes, including blood vessels (fig. 8 *A*). Such necrosis is sometimes total, resulting in a mass of debris in which no trace of the original lymphatic cells or reticulum can be recognized. It differs, however, from the homogeneous coagulation necrosis of tuberculosis. Nor is there any evidence of tubercle in the periphery of any of these foci. Stains for acid-fast bacilli are invariably negative. In other necrotic foci, one sees a meshwork of swollen eosinophilic fibers, resembling the structure of the fibrillar reticulum.

22. In 3 of these 5 cases, endocardial lesions were not present.

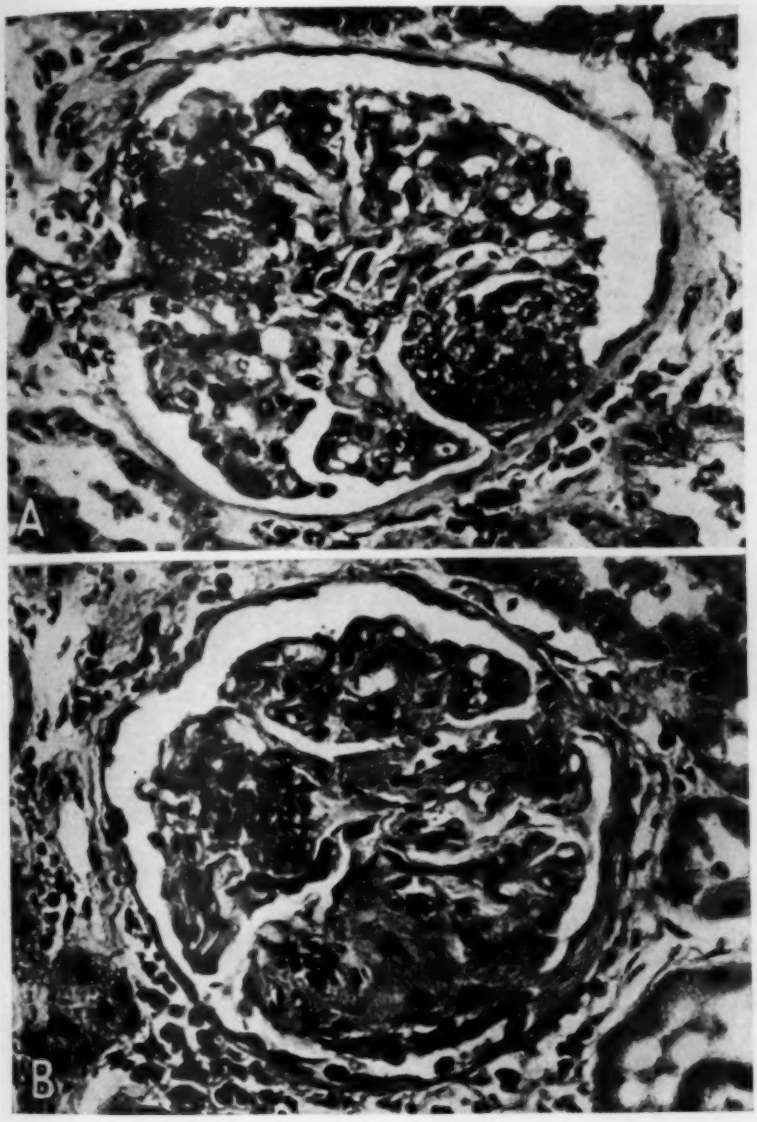

Fig. 7.—*A*, glomerulus showing focal necrosis of glomerular loops in the absence of the wire loop change. The necrotic loops become adherent to the capsule. No endocardial lesion was present in this case. *B*, glomerulus showing focal fibrosis of glomerulus. Focal necrosis and minimal wire loop change are also present. No endocardial lesion was found in this case.

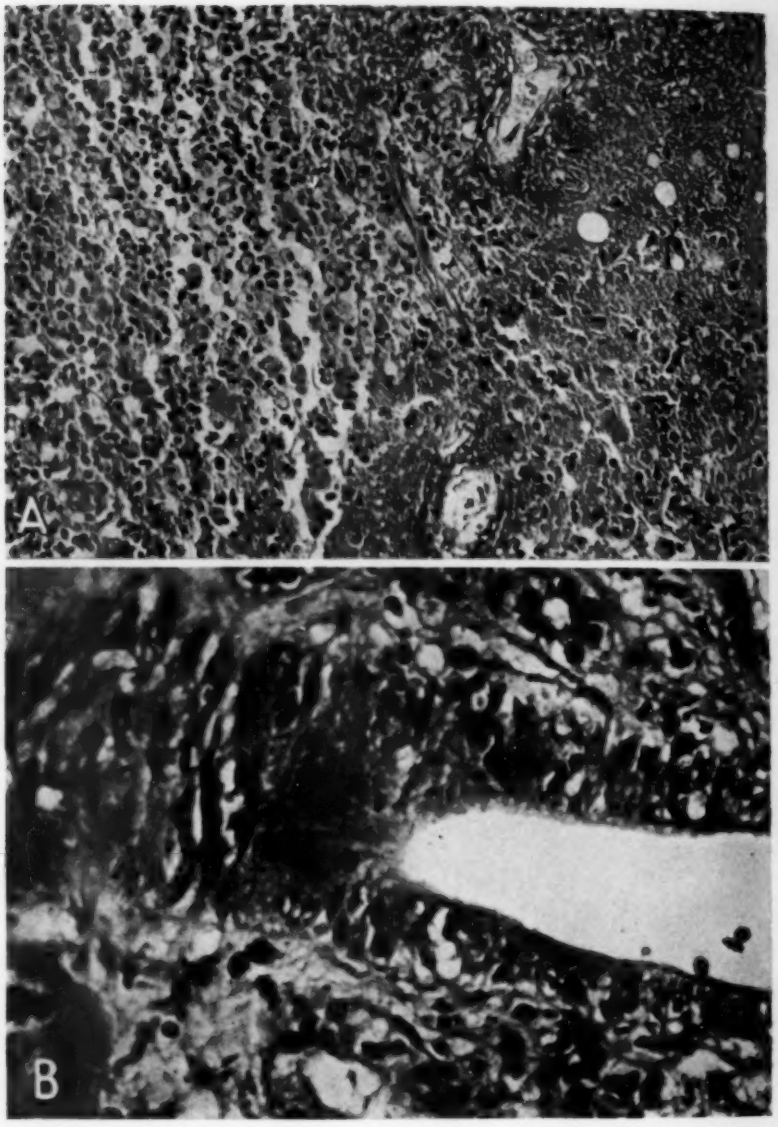

Fig. 8.—*A*, lymph node showing periphery of an area of necrosis of lymphatic tissue, including necrotic blood vessels. *B*, kidney showing focal fibrinoid degeneration and necrosis of collagen within the media of an interlobular artery.

This meshwork is devoid of lymphocytes but contains reticulum cells with distorted and pyknotic nuclei and macrophages laden with fat.

The connective tissue of the capsule and of the septums of the nodes occasionally shows the same collagen alterations described in other organs, associated with proliferation of fibroblasts. This may extend into the adjacent pericapsular fat tissue. Blood vessels both in the capsule and within the lymph nodes frequently show severe mural changes identical with those found in other organs. These will be described later. These vascular lesions are found not only in necrotic but in otherwise normal lymph nodes.

Blood Vessels.—Vascular lesions were encountered during histologic examination of the various organs. These alterations are described together. They were most frequent and most severe in the vessels of the kidneys but were found not infrequently in vessels of almost all the organs and tissues of the body, including those of the lesser circulation. In fact, in certain organs, such as those of the gastrointestinal tract, vascular alterations were the sole manifestations of injury of collagen. There was a considerable variation in the intensity and extent of vascular damage not only in the individual case but also in a comparison of case with case. In the most severe lesions there was complete necrosis of arteries and particularly of arterioles. In such lesions, which were frequently found in the kidneys but were observed also in other organs, the involvement of all the coats of the vessel wall precludes any analysis of the evolution of the lesion. Less severe alterations of vessel walls occurring in the same case in which necrotic lesions are found form a graduated series of vascular injuries lending itself to plausible analysis.

The mildest recognizable change is a deposit of homogeneous eosinophilic material (so-called fibrinoid) within the intima, between muscle fibers of the media or within the adventitia (fig. 8*B*). It is generally accompanied by fibroblast proliferation. In the intima this proliferation often results in considerable narrowing of the lumen without any participation of the endothelium. The newly formed fibroblasts generally exhibit degenerative changes as evidenced by distortion of the nuclei and by pyknosis.

Further progression of this process leads to involvement of more and more of the vessel wall so that in the intima complete rings of fibrinoid masses are laid down, lifting the endothelium from the media and choking the lumen. Intimal masses may fuse with medial masses across the elastic membrane. In turn, fusion with adventitial masses may follow (fig. 9*A*). With complete fibrinoid change of the collagenous framework of the vessel wall, destruction of muscular and elastic elements ensues (figs. 9*B* and 10*A*). In this phase there is a striking proliferation af adventitial cellular elements, which show degenerative changes.

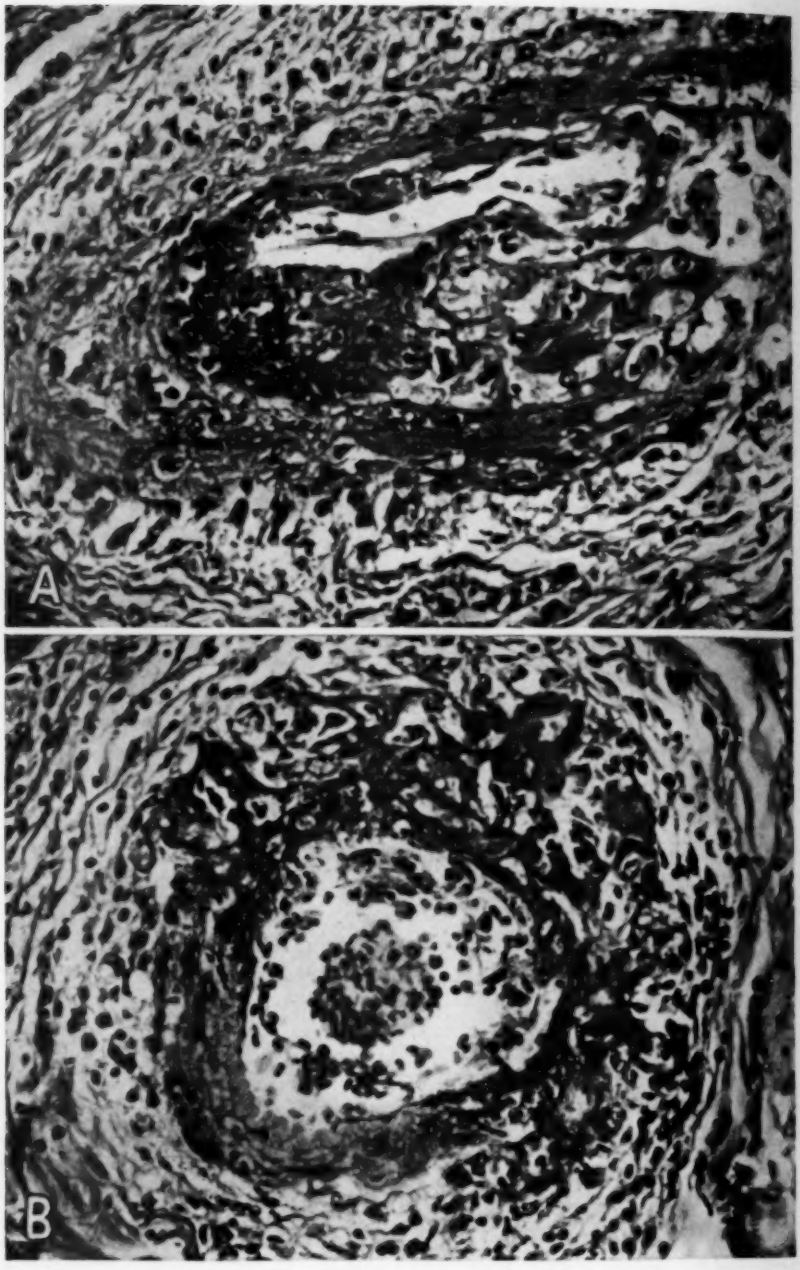

Fig. 9.—*A*, vagina showing fibrinoid necrosis of collagen within the intima, media and adventitia of a small artery. *B*, artery in appendix presenting massive fibrinoid necrosis with partial destruction of arterial wall, periarterial infiltration by polymorphonuclear leukocytes and lymphocytes and proliferation of adventitial cells.

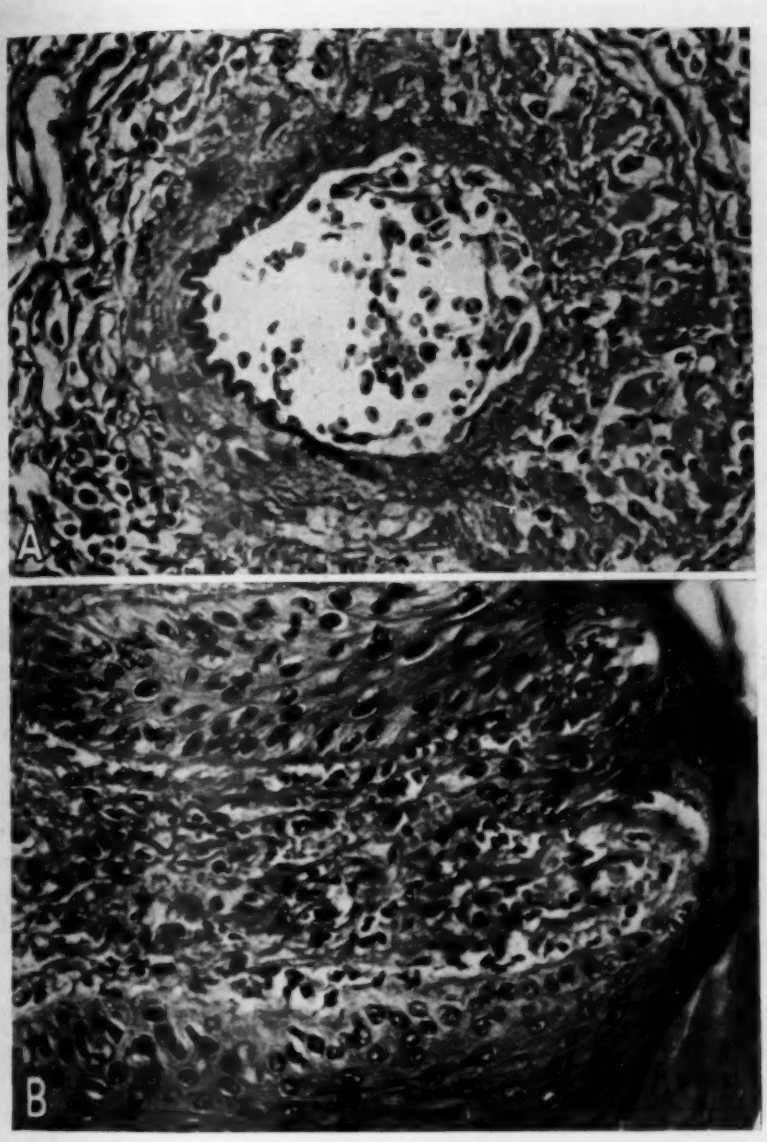

Fig. 10.—*A*, another section of the vessel shown in figure 9 *B*, stained for elastic fibers. *B*, skin showing fibrinoid degeneration of collagen within a papillary body. Note pyknosis and nuclear fragmentation of proliferated fibroblasts and capillary dilatation and extravasation of red blood cells.

In organs presenting the vascular lesions just described, other vessels may show cellular subendothelial intimal proliferation in the absence of or with very slight fibrinoid change. This proliferation is not to be confused with the type seen in malignant nephrosclerosis, since it lacks the concentric, rather fibrillar pattern of the latter. It may reach such proportions that the lumen is inordinately narrowed. Thrombosis secondary to this alteration in any of its phases is rare. Nevertheless, complete or nearly complete occlusion of involved vessels does occur, but almost always by massive swelling of the vessel wall rather than by formation of a thrombus. Furthermore, the proliferative changes are obviously not to be identified with organizing or completely organized thrombi. Their development can be traced through all stages as a process which is localized beneath the endothelium. This is true also in the precapillary arterioles and in the capillaries. In the former, fibrinoid masses, which may contain pyknotic nuclei, bulge into the lumen. This may simulate an organizing thrombus. In capillaries one can often find a complete ring of fibrinoid ensheathing the endothelium. This deposit cannot be dissociated from the basement membrane.

While in most cases the definitive necrosis of the vessel wall can be recognized as the most advanced phase of the series of fibrinoid changes just elaborated, we have, on the other hand, observed fulminating necrosis of the entire vessel wall not associated with fibrinoid.

In 3 cases fibrinoid change of the connective tissue of the walls of small and medium-sized arteries—up to the size of large interlobular arteries of the kidney—was associated with massive necrosis of the muscular and elastic lamellae of the walls. In these cases there was a striking inflammatory cellular reaction surrounding the necrotic foci and extending into the adventitia. Lymphocytes, plasma cells and a few polymorphonuclear leukocytes were found together with the proliferating adventitial cells. All of these cellular elements exhibited degenerative nuclear changes. The severity of the injury of the vessel wall was evidenced by the formation of small aneurysms, but no perivascular hemorrhage was seen. It is noteworthy that thrombosis is not found in the wake of even such damage. In the later stages the necrotic tissue is replaced by a cellular connective tissue. It is obvious that such lesions bear a striking resemblance to the necrotizing arteritis of Meyer's and Kussmaul's periarteritis nodosa.

In contrast to the arteriocapillary system, with its outstanding participation, the veins showed infrequent alterations. Moreover, in 3 cases in which fibrinoid degeneration was evident within the venous wall, analysis indicated that this change was merely an extension into the venous wall from the surrounding supporting tissue.

Skin.—Changes are encountered chiefly in the upper layers of the corium, particularly within the papillary bodies. The earliest change

is manifested as a homogenization of collagen fibrillae and ground substance in the most superficial (subepithelial) layer of the corium. However, the process advances beyond this stage (fig. 10 *B*). The ground substance and fibers undergo fibrinoid degeneration, as evidenced by eosinophilic clumping of the former and by irregular thickening and straightening of the latter together with the acquisition of increased acidophilia and refractility. In the most advanced lesion the clumped fibrinoid masses break up, and some of the fragments become basophilic. Similarly, some of the swollen fibers acquire an affinity for hematoxylin and also become fragmented. Fusion of such altered ground substance and fibers results in a conglomerate in which differentiation is not possible. Concomitant with the changes of fibers and ground substance there is proliferation of fibroblasts to a variable degree. These cells almost uniformly exhibit degenerative phenomena—distortion, pyknosis, necrosis. Dilatation of capillaries associated with extravasation of red blood cells is conspicuous and sometimes is the only histologic evidence of cutaneous involvement. In such instances, changes of collagen fibers and ground substance are not demonstrable with certainty. The fibroblasts, however, exhibit both proliferation and degenerative stigmas, which seem to indicate involvement of the connective tissue. The capillary endothelium is unaltered in the presence of this extravasation. Even in the more severe cutaneous lesions the capillary endothelium may remain intact in the presence of fibrinoid degeneration of its collagen wall (basement membrane) and adjacent connective tissue. It should be stressed that degenerative phenomena are inordinately prominent, while inflammatory cell infiltration is scant. Lesions of the larger vessels—arterioles and smaller arteries—follow the same pattern already detailed in the description of the vascular changes in other organs. Here again the vascular lesion is evidently determined by involvement of the connective tissue matrix of the corium which is continuous with the connective tissue of the vessel wall (fig. 11 *A*).

The fine elastic fibrillae of the superficial layer of the corium lose their affinity for the Weigert elastic fiber stain whenever they are caught in a focus of ground substance degeneration.

The epidermis often shows degenerative changes, such as vacuolation, progressing even to necrosis of the basal cell layer. This is seen also in the epithelial cells of the sweat glands. We consider these alterations as secondary to the much more pronounced changes in the connective tissue of the corium and its blood vessels.

Other Organs and Tissues.—No distinctive lesions are encountered in the specific elements of the various organ systems. Vascular lesions, as described (p. 591), are widely dispersed, occurring, however, much less frequently in organs other than the kidneys. Changes affecting the connective tissues similar to those seen in the pericardium are found not

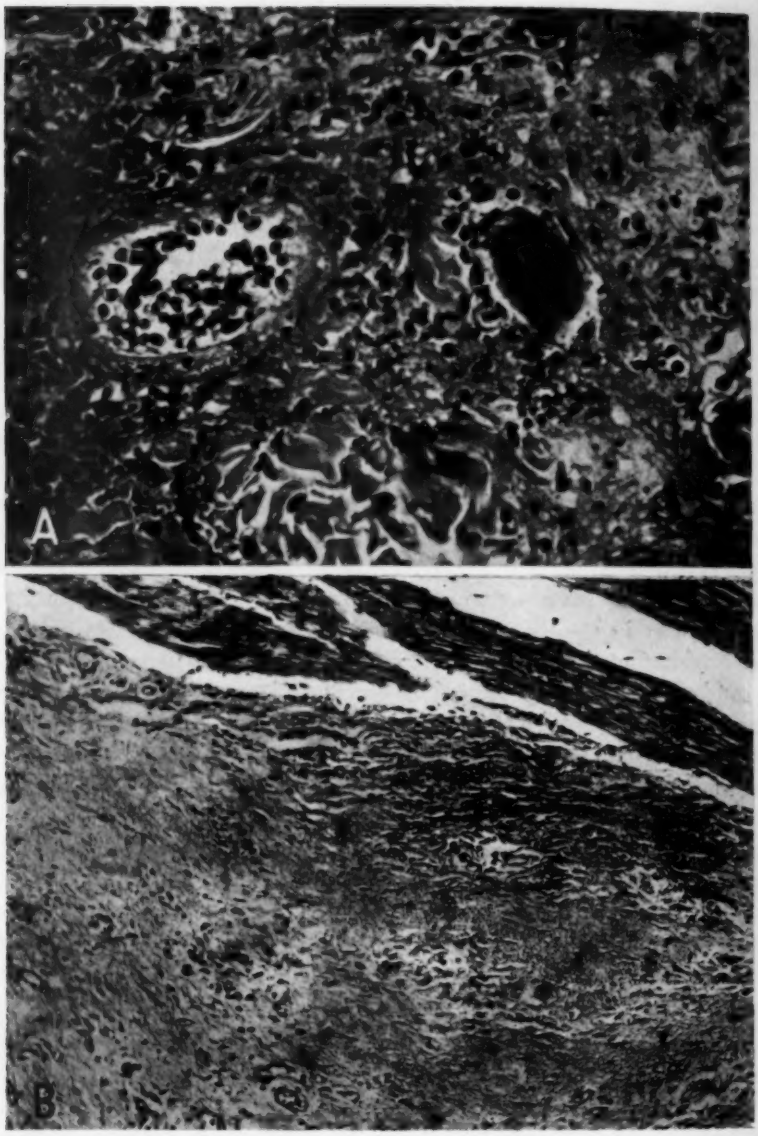

Fig. 11.—*A*, skin presenting fibrinoid degeneration and necrosis of collagen tissue of the corium with involvement of a vessel wall. *B*, mediastinal periesophageal tissue showing striking condensation of areolar tissue with focal fibrinoid degeneration of collagen and proliferation and degeneration of fibroblasts.

only in the stroma of the various organs but also in the great dispersed system of connective tissue of the retroperitoneum and mediastinum. In 2 cases the tissues of the posterior mediastinum were greatly thickened and densely adherent to the esophagus and trachea. The gross impression was that of chronic mediastinitis. Microscopically, these tissues presented the same series of alterations of fibers and ground substance (fig. 11 *B*) seen in the adhesive pericarditis already described. Similar histologic changes were found in routine sections of the retroperitoneal tissues, such as those adjacent to the adrenals, in several cases.

Skeletal muscle examined in 5 cases showed moderate perivascular round cell infiltration which was considered not significant. In a sixth case, however, there was intense interstitial and perivascular round cell infiltration associated with myolysis of the psoas and rectus muscles.

The bone marrow showed no changes of significance.

COMMENT

It is apparent that in our descriptions we have more or less limited ourselves to those features which in our opinion are distinctive. We have intentionally referred only briefly to such findings as we consider irrelevant and not essentially contributory to the identification of the disease. We have described in some detail certain conspicuous changes in the serous membranes, in the heart and blood vessels, in the kidneys, in the skin, in the spleen and in other tissues. In a superficial view these changes appear heterogeneous. After due analysis, however, it has become clear to us that this is not the case and that these apparently unrelated alterations must be regarded as the manifestations of an identical morbid process. This analysis resolves itself into two questions which demand answer. First, is there a common denominator in the localization of the process? Second, what is the nature of this process?

In the serous membranes, and particularly in the pericardium, we noted a series of alterations affecting the connective tissue. All elements of the connective tissue—cells, fibers and ground substance—show morphologic evidence of injury. The mucoid ground substance, ordinarily hardly visible, becomes evident as a swollen homogeneous interfibrillar mass. At the same time the fibers assume a straight, rigid and irregularly thickened appearance. They are deeply eosinophilic and highly refractile. These alterations, since Neumann, have been designated as fibrinoid degeneration of the connective tissue. The third element of the connective tissue—fibroblasts—give evidence of their participation by proliferation, degeneration and even necrosis. Gross [23] stressed the infiltration of large mononuclear cells and the active capil-

23. Gross, L.: Am. J. Path. **16**:375, 1940.

larization of the pericardium. While often conspicuous, these features are not sufficiently distinctive to be considered characteristic. Furthermore, we cannot agree with Gross that the "earliest pericardial changes appeared to involve the lining epithelium." On the contrary, the pericardial (as well as other serous membrane) involvement is from the beginning a relatively deep process by virtue of primary injury to the connective tissue. In contrast to the usual forms of inflammation of serous membranes, the alterative phase of the process is far out of proportion to the exudative. For instance, exudation is often absent even in the presence of conspicuous macroscopic thickening of the pericardium.

As we have indicated in our description, the earliest endocardial change encountered, both mural and valvular, is a subendothelial fibrinoid degeneration of the ground substance.[24] In more advanced lesions the fibers also undergo the same change. Fibroblast proliferation, degeneration and necrosis accompany the changes in fibers and ground substance. In the most advanced phase the connective tissue becomes completely necrotic, and basophilic fragments of nuclei, cytoplasm and fibers become set in the granular eosinophilic ground substance. Such foci are undoubtedly what Gross [25] characterized as "hematoxylin stained bodies" and described in great detail. He interpreted these as "pyknotic and karyorrhectic nuclear masses" and indicated that the lesion was the result of cellular destruction only, failing to recognize that this was but a part of a complex injury whose essential feature is the degeneration of the noncellular components of the collagenous tissues.

The alterations of the connective tissue of the myocardial septums are a histologic replica of those in the pericardium and endocardium, and although they are very characteristic, do not warrant separate discussion. They were seen in a third of the hearts and were conspicuous in individual cases. Gross [14] possibly saw the same lesion in one of his cases and pointed out that it "could be easily distinguished from true Aschoff bodies."

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24. Degenerated cellular elements, including the lining endothelium, are generally incorporated in the eosinophilic mass of ground substance. By the accretion of further altered ground substance the mass extends beyond the limits of the valve and appears on the surface as a microverruca. In serial sections the continuity of the mass with the valve may be lost. Such seemingly isolated structures may then resemble the "eosinophilic multinucleated coalescent bodies" so prominently stressed by Gross.[23] He considered them the result of "coalescence and desquamation en masse" of "plasma cells, young fibroblasts and endothelial cells." He did not, apparently, realize that the "eosinophilic hyaline or granular matrix" takes its origin from the injured ground substance, which is indeed the essential alteration.

25. Gross (footnotes 14 and 23).

It is apparent at this stage in the discussion that widespread damage is evident in all layers of the heart by virtue of a basic injury primarily localized in the connective tissues. These findings are opposed to the statement of Gross [23] that "the primary and fundamental change appears to be in the endothelium."

In the kidneys, the most outstanding and characteristic lesion is encountered in the glomeruli either as the wire loop change or as focal necrosis of loops. We have already indicated in our description that these two alterations are but separate phases of the same morphologic process. It becomes incumbent on us to determine the exact localization of the lesion in terms of the known elements of the glomerulus. The wire loop change can be dissociated both from the endothelium and from the epithelium. It is evident, then, that the focus of the change lies between these two structures. It is generally accepted that a well defined basement membrane separates endothelium from epithelium (Möllendorf [26]).

The basement membrane consists of a homogeneous ground substance containing fine silver-impregnated fibers (Bargmann [27]; Volterra [28]). Elaborating the concept of Zimmermann,[29] one may look on it as an attenuation of the connective tissue entering the glomerulus at the hilus. The physical appearance and the staining affinities of the "wire loop" suggest a relationship to the alterations of connective tissue already described. If we can identify the glomerular basement membrane with the collagen tissue ground substance in general, there can be no theoretic objection to the assumption that an injury which affects the latter may also affect the former. It follows, then, that in this disease, in which fibrinoid degeneration of the connective tissues at large is so fundamental, the "wire loop" can be considered nothing more than a peculiarly localized fibrinoid degeneration of ground substance. Similar to the more intensely injured endocardial connective tissue, in which fibrinoid degeneration proceeds to necrosis with inclusion of disintegrating regional cells, the necrotic glomerular loops also exhibit a compounding of fibrinoid with nuclear and cellular debris.

Although the "wire loops" have a rather uniform appearance in hematoxylin-eosin preparations, in trichrome stains, particularly the Mallory connective tissue stain, there are qualitative differences in the reaction of the altered basement membrane. At the one extreme it appears completely red; at the other, completely blue (Mallory), indicating fibrinoid degeneration on the one hand and collagenization on the other. Generally, the reaction is mixed.

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26. von Möllendorf, W.: Der Exkretionsapparat, in Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 1.
27. Bargmann, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **28**:99, 1938.
28. Volterra, M.: Ztschr. f. Zellforsch. u. mikr. Anat. **7**:135, 1928.
29. Zimmermann, K. W.: Ztschr. f. mikr.-anat. Forsch. **18**:520, 1929.

Occasionally we found fibrosis of portions of the glomerulus or of the total glomerulus. Were this not associated with the wire loop change, or with necrosis of loops, it could not be differentiated from the nonspecific end stage of other glomerular injuries. While this association of fibrosis with the active degeneration suggests that the former is the cicatricial end stage of the latter, one must consider the possibility that such fibrosis proceeds from the very beginning in its own right. This possibility is more evident in the periglomerular zone, in which active fibrosis is more frequently observed than fibrinoid degeneration.

Vascular lesions, while most often seen in the kidneys, are also observed rather frequently in other organs. Since these follow the same pattern wherever they are found, they should be discussed together.

Occasionally one sees thick rings of fibrinoid surrounding the endothelium of capillaries, replacing the normal delicate basement membrane. Such lesions are analogous to those glomerular lesions which we have characterized as "wire loops." The endothelium is apparently uninvolved. More frequently observed are lesions of the arterioles and small arteries.

As has already been seen, fibrinoid to a varying degree may appear anywhere in the vessel wall. The morphologic identity of these masses with those observed, for example, in the ground substance of the connective tissue of the heart suggests an origin out of the same matrix.

This is not unreasonable if one considers that a blood vessel consists of specific functional elements (endothelium, muscular fibers and elastic fibers) bound ther by a supporting framework of connective tissue. And it is this ue, primarily, which bears the brunt of injury in this disease. This i evident in the fibrinoid transformation of the ground substance and, urthermore, in the fibrinoid degeneration of collagen fibers in the adventitia.

This analysis of the vascular lesions must inevitably reduce them to a mere local expression of the fundamental connective tissue injury. In a morphogenetic sense, the vessel suffers injury only so far as it contains connective tissue.

The primary specific injury having thus been analyzed, definitive vascular necrosis may now be considered as the most severe phase of the connective tissue injury. In this most severe phase the injury of the supporting structure of the vessel wall necessarily entails degeneration and even necrosis of the muscular and elastic tissue components.

The proliferative phase of the injury to the vascular connective tissue is most conspicuous in the subendothelial zone of the intima and in the adventitia.

Endothelial alterations are not encountered concomitantly with early fibrinoid lesions. However, when accretion of subendothelial fibrinoid

is sufficient to produce bulging into the lumen, degeneration of the overlying endothelium may ensue. The resultant plug within the lumen cannot be distinguished from a thrombus. As indicated in their communication in 1935, Baehr, Klemperer and Schifrin [10] were misled by failure to realize the true origin of these plugs, regarding them as thrombi. This led them to stress the primary endothelial nature of the vascular injury. In the light of the foregoing analysis this idea is untenable.

The involvement of the connective tissue of the skin is less obtrusive than the injury of connective tissue in other organs, although that tissue forms in major part the structure of the integument as a whole. Fibrinoid degeneration of collagen fibers and ground substance is less conspicuous in the compact connective tissue of the corium than degeneration and necrosis of fibroblasts. The vasculature of the skin exhibits the same alterations which are evident elsewhere in the body.

This unity or identity of connective tissue alteration in the skin with that in other organs militates against any concept in which the cutaneous manifestations are considered as a toxic reaction to a visceral disease or, contrariwise, in which the visceral lesions are toxic manifestations of a cutaneous disease. We have seen that all the manifestations, whether cutaneous, cardiac, renal or vascular, are but varied expressions of a fundamental reaction of the connective tissue component of these organs.

Fibrinoid degeneration or connective tissue necrosis (blood vessels, capsule and trabeculae) is not conspicuous in the spleen. However, the peculiar periarterial sclerosis found in nearly every case is so arresting that it must be considered specific. We have not encountered a fully developed similar lesion in a wide variety of control cases. How is this type of alteration of connective tissue related to the degenerative process encountered so frequently in other organs? While fibrotic or sclerotic lesions are frequently associated with acute degenerative lesions in the renal glomeruli and periglomerular connective tissue, the converse is apparent in the periarterial zones of the spleen. In the kidney, the possibility exists that such sclerotic lesions represent terminal phases of the acute degenerative process. The great frequency of the sclerotic process in the face of very infrequent acute injury in the periarterial zones of the spleen leads us to believe that the process is a sclerosing one from the beginning. Apparently, the sclerosis which develops in this zone is in its own right a complete phenomenon, illustrating one type of response of the reticulum-collagen system. Thus far, then, we have encountered two types of alterations of collagen, namely, fibrinoid degeneration and sclerosis. Whether the affected collagen suffers the one alteration or the other may depend on the intensity and tempo of the injury. In one spleen the fibrinoid degeneration superimposed on individual sclerotic fibers of fully established fibrous periarterial rings suggested a sudden intensification of the morbid process.

The totality or universality of the morbid process is expressed in the involvement of connective tissue not only within the various organ systems but also within the great dispersed connective tissue of the body as a whole, such as that of the mediastinum and retroperitoneum.

At the outset of this discussion we posed two questions and applied them to an analysis of the pertinent alterations in the various organs and tissues in disseminated lupus erythematosus. We sought, first, to identify the substrate which was common to all those sites in which the morbid process was evident. Second, we attempted to analyze and characterize the morbid process wherever it was found. In the foregoing descriptions and discussion we have satisfied ourselves that the morbid process involves the connective tissues, be they functional (endocardium, glomeruli), stromal or part of the great dispersed system of filling and supporting tissues of the body. Furthermore, we have seen that the morbid process reveals itself in a series of alterations, chiefly degenerative, which recur again and again, in identical form, in the affected connective tissues.

Evidently, degeneration and necrosis of collagen as an isolated phenomenon is exceedingly frequent as an expression of direct injury in a variety of conditions. It occurs in the base of a peptic ulcer. It is found at the sites of pyogenic bacterial infections. It is seen in the vicinity of foreign body implantations—suture material, oils, hormone preparations, etc. The local character of these collagen changes and their obvious excitants serve to exclude them from any discussion of a disseminated disease of the collagen system.

There are, however, other diseases in which widespread injury of collagen plays an outstanding role. Thus, rheumatic fever and generalized scleroderma demand comparison and differentiation. Moreover, the extensive vascular alterations in periarteritis nodosa and in accelerated arteriosclerosis, as well as the glomerular lesions in diffuse and focal glomerulonephritis, exhibit undoubted similarities which necessitate discussion.

Libman and Sacks [13] and more recently Gross [23] have emphasized some of the criteria for differentiating the cardiac lesions of lupus erythematosus from those of rheumatic fever. Many of these are valid and valuable in establishing the identity of the one or the other. However, in attempting to characterize differences in morphogenetic terms, Gross made an error, we believe, in attributing the cardiac lesions in lupus erythematosus to a primary injury of endothelium in contrast to the primary injury of collagen in the rheumatic heart. Our observations lead us to believe that the injury of collagen is as fundamental to the alterations of the heart in lupus erythematosus as it is to the cardiac lesions in rheumatic fever. In fact, the extent and severity of the alterations of collagen in the heart in lupus erythematosus serve in part to differentiate

both entities. This is evidenced by the frequency of actual valvular necrosis in lupus erythematosus in contrast to the rarity of that condition in rheumatism. This has also been stressed by Gross.

The differences become more manifest if one regards not only the less intense injury of collagen in rheumatic fever but also the more striking and qualitatively different cell response. The large, actively proliferating Aschoff cells are never found in lupus erythematosus. In the latter, proliferating fibroblasts almost always exhibit striking degenerative changes, while in rheumatism, especially in the cardiac valves, the fibroblast proliferation is progressive and almost from the beginning associated with the production of new fibrous tissue. Finally, the dominance of the degenerative over the productive phase of collagen alteration in lupus erythematosus is nowhere better illustrated than in the myocardium, where a maximal injury of collagen fibers is seen with frustrated fibroblast proliferation; whereas in rheumatism, relatively mild collagen degeneration is accompanied by a most arresting proliferation of the large Aschoff cells.

Obviously, there should be no confusion of the involvement of the heart in lupus erythematosus with subacute bacterial endocarditis. Libman and Sacks [13] have discussed the differential diagnosis quite adequately.

The widespread involvement of blood vessels in lupus erythematosus imposes on us the necessity of comparing this disease with periarteritis nodosa in which vascular involvement is, in fact, the fundamental feature. Intense degeneration of collagen in the arteries is essential in both diseases. In both the damage of the collagen in the vessel wall may lead to total necrosis. In periarteritis nodosa, in contrast to lupus erythematosus, such degeneration or necrosis is accompanied by a most conspicuous inflammatory reaction in which the participation of eosinophils is noteworthy. As a rule, in periarteritis nodosa vessels of larger caliber suffer the greatest damage, while smaller vessels and even capillaries may occasionally be affected. The converse is true of the vascular involvement in lupus erythematosus, in which the rule is: predominant damage of the smaller arteries and capillaries with only infrequent participation of the medium-sized vessels. In the last, the similarity of the lesions may even suggest periarteritis nodosa microscopically.

The massive destruction of the blood vessel wall leading to hemorrhage, on the one hand, or to aneurysm formation, on the other, is a feature par excellence in periarteritis nodosa. This does not occur in lupus erythematosus except for aneurysms observed only microscopically in a few of the larger arteries. The basis for these aneurysms may lie in the larger caliber of the vessels involved and the correspondingly higher blood pressure in such vessels. Furthermore, the aneurysms appear to be associated with extreme necrosis of the vessel wall. The latter fact may

also account for the frequent occurrence of thrombosis in periarteritis nodosa, rare in the arterial lesions of lupus erythematosus.

While the vascular lesions in both diseases may be differentiated (severity and localization), they are nevertheless fundamentally similar so far as primary damage of collagen underlies the definitive vascular alteration. In lupus erythematosus the participation of vessels represents but one phase of a general involvement of the connective tissues. The vascular alterations in periarteritis nodosa have never been considered from this point of view. The association of periarteritis nodosa with rheumatic fever, a disease of widespread implication of collagen, has been described by Friedberg and Gross.[30] In their cases the occurrence of collagen alterations outside the peripheral blood vessels, namely, the characteristic endocarditis and specific myocarditis, is noteworthy. These collagen changes are, however, specific and cannot be dissociated from rheumatic fever. Such observations do not, therefore, serve to illustrate the occurrence in periarteritis nodosa of collagen alterations apart from the blood vessels. There are, nevertheless, a small number of cases of the latter disease in which extravascular collagen alterations are found. Microscopically, endocardial fibrinoid degeneration indistinguishable from that seen in lupus erythematosus may be found, although in none of these instances is the striking gross appearance of the endocardial lesion present as described by Libman and Sacks.[13] In only one of our cases of periarteritis nodosa was necrosis of collagen found outside the cardiovascular system. In this case the retroperitoneal and subcutaneous tissues exhibited nodular foci of fragmented masses of deeply eosinophilic and basophilic collagen tissue surrounded by large cells having hyperchromatic nuclei and basophilic cytoplasm. The peculiar nodular character of the necrotic collagen and the type of cellular reaction serve to differentiate the injury of collagen described here from that observed in corresponding sites in lupus erythematosus.

Since the renal glomerular lesion in lupus erythematosus—the "wire loop"—is so striking, we must determine whether identical changes can be found in the kidney in any other condition. Obviously, glomerulonephritis presents itself for investigation. In examining an unselected group of cases of subacute and chronic glomerulonephritis, 43 in all, we encountered the wire loop change five times. Such "wire loops" were always associated with the characteristic glomerular alterations of nephritis, such as leukocytic infiltration, proliferation of endothelial and epithelial cells and more or less advanced fibrosis of the tufts. The nephritic glomerular changes were dominant by far and of course there were corresponding changes in the tubular apparatus. By contrast, in our series of 20 cases of lupus erythematosus the changes of glomerulo-

30. Friedberg, C. K., and Gross, L.: Arch. Int. Med. **54**:170, 1934.

nephritis were encountered but twice. The "wire loops" seen in nephritis are tinctorially and configuratively, as far as we can determine, identical with those found in lupus erythematosus. It is important to stress that this type of loop alteration cannot and should not be confused with the hyaline thickening and fusion of loops so frequently encountered in the later stages of glomerulonephritis (or even in the arteriosclerotic kidney). The occurrence of such "wire loops" in glomerulonephritis is not surprising if one recognizes that they are a morphologic expression of degeneration of the collagenous capillary basement membranes. Glomerulonephritis, in common with other inflammations, presents three faces—alteration, exudation and proliferation. In glomerulonephritis, exudation and proliferation overshadow alteration. In fact, in most of the cases alterative phenomena are morphologically not discoverable. In the 5 cases of glomerulonephritis in which "wire loops" were found, these were associated with far more conspicuous exudative and proliferative phenomena. The "wire loops" in glomerulonephritis therefore represent but one component of the total inflammatory triad. By contrast, the "wire loops" of lupus erythematosus are generally not associated with exudation and proliferation but represent a primary and fundamental collagen degeneration which is similarly expressed in other organs. This cannot be demonstrated in glomerulonephritis.

The focal necrosis of glomerular loops in lupus erythematosus represents, as we have already indicated, an exaggerated form of the same degenerative process that is responsible for the "wire loop." It should not, therefore, be confused with the focal glomerular lesions seen in the kidneys during the bacterial phase of subacute bacterial endocarditis. Characteristic of the glomerular lesion in the latter disease is a massive necrosis involving all the elements of the affected loops. This generally elicits a conspicuous proliferation of visceral epithelial cells. "Wire loops" are never seen.

Attention has repeatedly been called to the thickening of the renal glomerular loops in eclampsia. In studying our own eclampsia material, we have indeed observed loop thickening. This alteration is difficult of analysis. Nevertheless, it bears no resemblance to the "wire loop" change of lupus erythematosus. The glomerulus in eclampsia is characterized by an apparent fusion of loops, which appears to be due largely to degeneration and swelling of the glomerular epithelial cells. The discrete pattern of individual loops is therefore obliterated. Within the bulky mass of fused loops, foci of massive epithelial hyaline droplet degeneration taking an intense eosin stain may bear a superficial resemblance to the deeply eosinophilic altered basement membrane in the glomeruli showing the wire loop change of lupus erythematosus. Hence, in the latter the glomerular loops are, indeed, rendered more distinct, while in eclampsia the skeinlike appearance of the glomerulus is lost.

The greatest similarity to the wire loop change in the glomerulus is seen in hematoxylin-eosin preparations of early renal amyloidosis. This condition is, of course, easily excluded by the special stains for amyloid.

The glomerular changes in arteriosclerosis demand consideration. But these cannot be dissociated from the vascular alterations with which they are always linked. In so-called benign arteriosclerosis the hyalinization of discrete glomerular loops may occasionally be so striking as to simulate wire loops. Even here, however, the eosinophilia of the thickened loops, particularly in formaldehyde-fixed material, is not so intense as that of the altered basement membrane of the "wire loop" of lupus erythematosus. Furthermore, in azan-stained sections the thickened glomerular loops of arteriosclerosis are always uniformly blue, whereas the "wire loops" appear either partially or completely red. Finally, the total picture of the arteriosclerotic kidney, both gross and microscopic, differs so materially that confusion is hardly to be expected.

By the same token, the kidney of malignant nephrosclerosis ought not to be confused with that of lupus erythematosus. However, the severe vascular lesions in the former condition, which are conspicuous in other organs as well as in the kidneys, must be compared with those in lupus erythematosus. In both diseases necrosis of arterioles is found. In malignant nephrosclerosis arteriolar necrosis is either associated with or preceded by a homogeneous hyalinization of the entire vessel wall. Early necrosis becomes evident by the migration of red blood cells into the homogenized vessel wall, and definitive necrosis, characterized by actual hemorrhagic infarction of the vessel itself, supervenes. An indistinguishable end result may be established in lupus erythematosus not by necrosis within an already hyalinized vessel but by fibrinoid necrosis occurring in a previously normal vessel.

The necrosis of glomerular loops in malignant nephrosclerosis differs materially from that seen in lupus erythematosus. The necrotic loops in the latter generally exhibit evidence of the characteristic damage of collagen (wire loop). This is lacking in malignant nephrosclerosis, in which necrosis occurs in glomeruli showing little or no evidence of previous alteration. At any rate, one never finds any glomerular change comparable to the "wire loop" of lupus erythematosus.

In summarizing the latter discussion we must submit that the morphologic aspects of fully developed vascular necrosis obtaining in accelerated arteriosclerosis and in lupus erythematosus are indistinguishable. The differences in the morphogenesis of such necrosis in the two diseases, however, point to a fundamental dissimilarity of morbid process. It should be unnecessary to reemphasize at this point in the discussion the basic fact that the vascular lesions in lupus erythematosus reflect only part of a generalized disturbance of the collagen system.

From the preceding analysis we have seen that the morbid process in lupus erythematosus revolves about a well defined disturbance of collagen affecting all organs and tissues of the body. The essentially degenerative nature of this disturbance is expressed in its most striking form in an alteration to which Neumann [19] applied the term "fibrinoid degeneration." The nature of this alteration has been the subject of extensive investigations, and its analysis has been exhausted from the purely morphologic approach by Klinge,[31] Bahrmann [32] and others. We believe that any further elucidation of this frequent pathologic phenomenon will be effected only by attacks other than morphologic. We must stress, however, that fibrinoid degeneration, be it found in fibers or in ground substance, should not be confused with simple exudation of fibrin; it represents a profound physicochemical alteration of collagenous tissue. While fibrinoid degeneration is the most spectacular expression of this alteration in lupus erythematosus, the disturbance may also, to a lesser degree, manifest itself in sclerosis of collagen. This is particularly evident in the splenic lesions.

Fibrinoid degeneration of collagen is a well known and common morbid process. Neumann [19] found it as a frequent alteration in inflammation. Askanasy [33] described it in the base of peptic ulcers of the duodenum and stomach. Ricker [34] alluded to the same alteration in the connective tissue of tumors and of hygromas. Schosnig [35] pointed out its occurrence in a variety of nonspecific and specific inflammations.

In view of such observations one may question our attaching such great significance to an apparently nonspecific lesion. It must be emphasized, however, that in every instance in which fibrinoid degeneration of collagen is found in the observations just mentioned, two important conditions obtain: first, the alteration is always local; second, it is always identified with a direct local injury. This may be caused by bacteria or their toxins, by chemical agents or by lack of blood supply.

This is in sharp contrast to the systemic occurrence of the alterations of collagen in lupus erythematosus, in the absence of a palpable injurious agent.

It may be argued, therefore, that such alterations may be the expression of a hypersensitive state. Gerlach,[36] working with the Arthus phenomenon, described the swelling of collagen fibers (fibrinoid degeneration) as an essential feature of hyperergic inflammation. The concept of hypersensitiveness has been accepted by many as the basis

31. Klinge, F.: Ergebn. d. allg. Path. u. path. Anat. **27**:1, 1933.
32. Bahrmann, E.: Virchows Arch. f. path. Anat. **300**:342, 1937.
33. Askanasy, M.: Virchows Arch. f. path. Anat. **234**:111, 1931.
34. Ricker, G.: Virchows Arch. f. path. Anat. **163**:44, 1901.
35. Schosnig, F.: Virchows Arch. f. path. Anat. **286**:291, 1932.
36. Gerlach, W.: Virchows Arch. f. path. Anat. **247**:294, 1923.

of the tissue reactions in periarteritis nodosa. We have already compared lupus erythematosus and periarteritis nodosa from the morphologic point of view and have seen that while fibrinoid degeneration of collagen is common to both diseases, in the latter it is restricted to the vascular system. Furthermore, the classic clinical evidences of hypersensitivity so frequently observed in periarteritis nodosa are lacking in disseminated lupus erythematosus.

It would be a mistake, therefore, to speak glibly of lupus erythematosus as an allergic disease—at least in the narrow sense of the term.

A widespread involvement of the collagen system is seen also in rheumatic fever. We have already compared this disease with disseminated lupus erythematosus and have noted that the localization of the collagen alterations in the two diseases exhibits great differences. And even were the localization identical, we should still contend with a striking difference in the evolution of the collagen change. Whereas in lupus erythematosus the collagen disturbance is progressively degenerative, in rheumatic fever even a minimal degeneration of collagen is associated with a most conspicuous cellular reaction, which is, moreover, specific.

Setting aside for the moment any consideration of cause, we must conclude that collagen degeneration of a progressive nature, widespread throughout the body and having at the same time characteristic local expression (as seen in the glomeruli, in the myocardium and other tissues) forms the morphologic basis for the morbid process called disseminated lupus erythematosus.

From this premise it must follow that previous morphologic characterizations of lupus erythematosus are not acceptable, since they lacked both recognition and comprehension of the fundamental lesion. Thus, dermatologists, such as Montgomery,[37] consider the visceral lesions in disseminated lupus erythematosus as mere toxic manifestations of a cutaneous disease. Although Montgomery conceded the possible specificity of the cardiac and renal lesions, he failed to link them to the cutaneous alterations. Indeed, he could not make this association since he did not recognize their common denominator.

Conversely, Libman and Sacks [13] correlated the unique endocarditis with cutaneous lesions characteristic of lupus erythematosus and made an important contribution in distinguishing the associated clinical syndrome from rheumatic fever, on the one hand, and from subacute bacterial endocarditis, on the other. On the anatomic side, however, they failed to analyze the morbid process. The unfortunate result has been an undue emphasis on the cardiac lesions. This inordinate pre-

37. Montgomery, H.: J. Invest. Dermat. **2**:343, 1939.

occupation with the heart has, in fact, led to the anatomic conception of a morbid process affecting the heart primarily (Gross). This, we have shown, it certainly is not.

Although Gross [23] admitted the occurrence of changes in other organs, he made no attempt to analyze these changes in relation to the cardiac lesions.

Baehr, Klemperer and Schifrin [10] observed widespread vascular lesions which they thought to be characteristic of lupus erythematosus and attempted to unify the changes in the heart, blood vessels and serous membranes on the basis of a primary endothelial injury. In the light of the findings presented in this communication such a concept is untenable. Although vascular alterations in the skin, kidneys and other organs were emphasized in that report and are responsible for some of the clinical manifestations on which the diagnosis of the disease is predicated, they can be regarded only as an expression of the fundamental morbid process affecting all the collagenous tissues.

The object of this investigation was to circumscribe acute lupus erythematosus in morphologic terms. We believe this object has been attained with the exception of the synovial membranes and the central nervous system, material of which was not available to us.

The widespread, frequent and characteristic alteration of collagen together with the special predilection of the injury for the collagen in certain sites (heart, glomeruli, blood vessels, skin, spleen and retroperitoneal tissues) has been seen in no other disease save diffuse scleroderma.[38]

Having thus presented an anatomic definition of lupus erythematosus, we are confronted with the question of cause. How far can our purely morphologic observations contribute to the solution of this problem? The histologic alterations are not those commonly encountered in infectious disease. The primarily and predominantly degenerative nature of the lesions is in contrast to the picture of inflammation, whether acute or granulomatous, which generally obtains in infections. Moreover, aside from superimposed complications, organisms are not discoverable.

The infrequency of arrested tuberculosis and the complete absence of active tuberculosis in our material make it unnecessary to consider that the tissue changes represent an unusual reaction to tuberculous infection.

Speculations as to etiology are not germane to the purpose of this paper. Elucidation must depend on new clinical and experimental investigations. We hope that these morphologic observations may serve as a groundwork for further progress in these directions.

38. One of us (Pollack, A. D.: Arch. Path. **29**:859, 1940) has called attention to identical collagen changes in scleroderma. A detailed description and discussion will be given in another paper.

SUMMARY

Disseminated lupus erythematosus is founded morphologically on a well defined series of alterations of the collagenous tissues. The characteristic organic changes, previously considered as heterogeneous, can now be understood as local manifestations of the widespread damage of collagen. Various concepts of lupus erythematosus as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation can be entertained no longer.

ABSTRACTS OF CASES

CASE 1.—A 17½ year old white girl was in apparent good health until eighteen months before her entrance to the Mount Sinai Hospital. At that time she was ill for a month with swelling of the knees and ankles and fever. During the subsequent nine months she felt weak, had some stiffness in the knees and ate only fairly but had no fever. She then became ill again with fever. She was admitted to another hospital, where a reddish brown rash appeared over both cheek bones. After several weeks she improved somewhat and went to the country early in June. Against advice, she exposed herself to the sun. Following this, she became rapidly worse, and the rash became more florid. During a second hospitalization there was a convulsion. She lost large amounts of hair. After she had been in the hospital five weeks the rash faded. When she returned home, she felt stronger. Six weeks before her admission to the Mount Sinai Hospital, she caught cold, and her fever returned. The rash reappeared on the face and spread to the arms, trunk and lower extremities. Her appetite vanished, and she became progressively weaker. She had a cough. One week before admission the first of a series of convulsive seizures took place, characterized by sudden rigidity of the body, upward deviation of the eyeballs, tetanic contraction of the upper extremities, frothing at the mouth and loss of sphincteric control. These seizures increased in frequency so that on the day before admission she had ten, each lasting about ten minutes.

On examination she appeared well developed and well nourished. The temperature was 104 F. She was acutely ill and hallucinated. The face, neck, upper anterior part of the thorax and distal parts of the extremities were the sites of grayish white scaly erythematous, or ulcerated and weeping, confluent patches. On the abdomen a brownish macular nonscaling eruption was noted. The hair on the head was markedly thinned out. The chest signs were normal. The heart was not enlarged. The blood pressure was 110 systolic and 70 diastolic. The heart rate was 120. The abdomen was soft and slightly distended. The right knee was slightly warm, swollen and tender. The neurologic examination disclosed nothing save that the head was slightly retracted. There was no enlargement of superficial lymph nodes.

Shortly after admission she had a seizure characterized by deviation of the eyes to the left, twitching of the right leg and general rigidity. She died soon after.

Anatomic Diagnosis.—Disseminated lupus erythematosus; focal necrosis of abdominal lymph nodes with secondary suppuration and infected ascites (Str. haemolyticus); focal necrosis of the spleen; focal fibrinous pericarditis; fibrous pleural adhesions; chronic perihepatitis and perisplenitis; fatty change of the liver.

CASE 2.—A 23 year old white woman became ill five months before her entry into the hospital with mild fever and weakness. Shortly thereafter examination of the

urine revealed albumin (4 plus), red blood cells and white blood cells. Within a few weeks, anorexia, vomiting, abdominal cramps and slight fever developed. These symptoms subsided about three months prior to admission. Following not too excessive exposure to the sun, a red eruption appeared over the cheek bones and the bridge of the nose. The hair of the head began to fall out. The other symptoms recurred. Two weeks before coming to the hospital she noticed spots before the eyes. The fever returned, the temperature rising to 103-104 F. Puffiness of the eyelids appeared. There were a nonproductive cough, extreme fatigue and drowsiness.

Examination revealed an acutely ill asthenic febrile woman, breathing rapidly and, on slight exertion in bed, with difficulty. There was well marked edema of the face, especially of the eyelids. The eruption of acute lupus erythematosus was seen on the nose and cheeks. The hair of the head and eyebrows was sparse. The ocular fundi showed blurring of the nasal margins of the disks; the arteries were prominent and indented the veins; there were recent and old exudates and rare hemmorrhages. There were a few red papules on the soft palate. The superficial lymph nodes were slightly enlarged. The lungs were clear. The heart was not enlarged. The sounds were muffled. There was a protodiastolic gallop rhythm at the apex. A faint systolic murmur was heard at apex and base. The pulmonic second sound was accentuated and split. The blood pressure was 122 systolic and 70 diastolic. The edge of the liver was palpable 2 fingerbreadths below the margin of the ribs. The spleen was not felt. Slight sacral edema was noted.

The hemoglobin content was 56 per cent; the red blood cell count, 3,420,000; the white blood cell count, 4,200, with 72 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 8 per cent mononuclears and 1 per cent basophils. The platelet count was 200,000. The sedimentation time was twenty-two minutes. The urine showed a specific gravity of 1.010, albumin (3 plus), a few waxy, granular and cellular casts and 1 to 2 red blood cells and 5 white blood cells per high power field. The blood urea nitrogen was 34 mg., calcium 7.5 mg. and phosphorus 3.2 mg. per hundred cubic centimeters. The blood albumin was 3.0 Gm., globulin 0.8 Gm. and total protein 3.8 Gm. per hundred cubic centimeters. The Wassermann test of the blood was negative. The carbon dioxide–combining power was 38.8 volumes per cent. The electrocardiogram showed low voltage of the QRS complexes.

During the first two weeks in the hospital the patient had an irregular elevation of the temperature up to 104 F. Gross myoclonic twitchings were present in the upper and lower extremities. Examination of the central nervous system revealed no evidence of intrinsic disease. There were repeated attacks of severe cramps in the right lower region of the abdomen, sometimes associated with vomiting. The hemoglobin fell to 47 per cent, and repeated transfusions were required.

Unilateral parotitis developed. This subsided after treatment with roentgen rays of high voltage.

During the second month troublesome furunculosis developed over the back. This subsided after local treatment. Erythematous lesions appeared on the hands and chest. Marked albuminuria, together with the presence of casts, erythrocytes and white cells in the urine, persisted. The specific gravity remained fixed, and there was slight azotemia. Leukopenia persisted. The blood pressure varied between 124 systolic and 90 diastolic and 160 systolic and 100 diastolic.

Near the end of the second month there was transient arthritis of the right knee. Vision became progressively worse concomitantly with progression of the eyeground changes.

During the third month the patient's condition became gradually worse, a trend that was continuous to the time of her death. There were repeated attacks of generalized abdominal colic, refractory to all sedative and antispasmodic drugs save morphine. Anorexia was severe, and there was also dysphagia and frequent vomiting. A complete study of the gastrointestinal tract by roentgenography disclosed no abnormality. The edema progressed to anasarca. The facial eruption spread over the entire face. There were no signs of pulmonary or pleural involvement. A loud systolic murmur appeared at the apex of the heart. The blood urea nitrogen remained at about 30 mg. per hundred cubic centimeters. The furunculosis of the back (Staph. aureus) recurred. During the last week, the temperature rose to 106 F. The patient became delirious, general convulsive movements developed and death with pulmonary edema followed.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis of the mitral and tricuspid valves and of the right and left ventricles; superimposed acute bacterial endocarditis (Staph. aureus); multiple hematogenous abscesses of the kidneys, liver, spleen, myocardium and intestines; moderate hypertrophy and dilatation of the left ventricle; focal atelectasis of the lungs; ascites; subcutaneous edema of the back; status after incision and drainage of a furuncle of the back.

Case 3.—A 21 year old native-born white woman complained of polyarthritis of four months' duration. She had had scarlet fever at the age of 13 and chorea at the age of 11. Six months before admission she was treated with salves for a generalized papular eruption said to have been "ringworm." Two months later she began to have pain, swelling and tenderness in both wrist joints. Soon there was involvement of the elbows, knees, fingers, left shoulder and ankles. Except for the wrists, the joints were not swollen. The pain was intermittent. One week before admission she was seen by a physician, who found abnormalities of the urine. Over a period of six months she noted a malar flush following exposure to sunlight.

Physical examination revealed a well developed but chronically ill young woman in no acute distress. The temperature was 101.6 F.; the pulse rate, 88; the respirations, 20. Oven the malar eminences was a nonerythematous papular eruption. The skin was sallow. There were small depigmented areas on the trunk and hands. Old and recent ecchymoses were seen in the left antecubital fossa and over the malleoli. Over the abdomen, lower part of the thorax and extremities were slightly raised discrete multiform erythematous blotches. Petechiae were present in the conjunctivas. The fundi were normal. There was a small hemorrhage in the buccal mucosa. The thyroid was diffusely enlarged and resilient. The lungs were clear. The heart was not enlarged. There were a faint presystolic thrill and a rough presystolic apical murmur. The blood pressure was 120 systolic and 80 diastolic. The spleen was palpable 1 fingerbreadth below the costal margin. The superficial lymph nodes were enlarged. The right wrist was swollen and tender. There was fusiform deformity of the phalanges.

The hemoglobin content was 65 per cent; the red blood cell count, 3,440,000; the white blood cell count, 3,100, with 55 per cent neutrophilic leukocytes, 36 per cent lymphocytes, 7 per cent monocytes, 1 per cent basophils and 1 per cent plasma cells. The blood platelet count was 100,000; the bleeding time was four minutes and the clotting time twelve minutes, with good clot retraction. The tourniquet test was negative. The sedimentation time was twenty-eight minutes. The urine contained a trace of albumin, many granular casts and a few red and white blood

cells. The blood urea nitrogen was 39 mg., calcium 9.2 mg., phosphorus 4.2 mg., total protein 6.3 Gm., albumin 4.5 Gm. and globulin 1.8 Gm. per hundred cubic centimeters. Blood for the Wassermann test was anticomplementary; the Kahn test was negative. Blood cultures were negative. A concentration test revealed specific gravity up to 1.020.

The patient was given blood transfusions and treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). In the second week she became extremely cyanotic, with rapid heart action and gallop rhythm. The blood urea nitrogen rose to 108 mg. per hundred cubic centimeters. The administration of sulfapyridine was stopped. Cardiac failure progressed. Chvostek's sign appeared. In spite of repeated blood transfusions, the hemoglobin continued to fall. The temperature ranged as high as 105 F. The urine was examined for abnormal porphyrin, with negative results. A trial course of testosterone propionate had no influence on the course of the illness. In the second month signs of pericarditis together with signs of fluid in the left pleural space appeared. At the same time a full blown butterfly-shaped erythematous rash typical of lupus erythematosus developed over the nose and cheeks. The patient improved transiently, and the blood urea nitrogen returned to normal. The facial eruption waxed and waned. Decubitus ulcers appeared over the buttocks. In the third month the patient's hair began to fall out. The urine always contained albumin, red cells, white cells and casts. She continued to show signs of congestive heart failure. The electrocardiogram exhibited evidence of myocardial damage. Bilateral suppurative parotitis developed later, necessitating surgical drainage. The patient died in congestive heart failure. At the time of death she was quite cachectic.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving all valves and the right and left ventricles and the left auricle; superimposed bacterial endocarditis of the mitral valve (Str. haemolyticus); focal bronchopneumonia of the lower lobes; moderate dilatation of all cardiac chambers and moderate hypertrophy of the left ventricle; peritoneal and pleural effusions; fibrinous and fibrous pericarditis; fibrinous perisplenitis and perihepatitis; Zahn's infarct of the liver; focal necrosis of the liver; infarct of the spleen; uric acid nephrolithiasis; bilateral purulent parotitis; status seven days after incision and drainage of bilateral parotitis; otitis media; icterus; emaciation; sacral decubitus ulcer; suprapubic ulcer of skin.

Case 4.—The patient was a 32 year old native-born white woman. The family history and the personal history were not remarkable. Nine years before coming to the hospital she consulted a dermatologist because of a flat red eruption over the bridge of the nose. He diagnosed lupus erythematosus and treated her with a gold compound. Within a year, the eruption faded entirely. During each of the following three summers, however, the eruption returned. It was more widespread. In addition to recurrence in butterfly pattern over the bridge of the nose and cheeks, it had spread to the ears, scalp and neck. Coincidentally with the appearance of the lesions on the scalp, she lost the hair in two large patches behind the ears. There was no fever or systemic manifestations with these recurrent attacks. The gold salt therapy was repeated with an apparent good result at each recurrence. Two years before admission she was confined to bed for six weeks with migratory pain and tenderness in the knee, ankle, elbow and proximal interphalangeal joints. She was slightly feverish. There was no exacerbation of the cutaneous lesions. One year later, after a free interval of four years, there was a recurrence of the cutaneous eruption after careless exposure to the

sun. Gold salt therapy was instituted again. Shortly thereafter oral lesions appeared for the first time. Although the cutaneous and oral lesions improved, she continued to feel bad, and eight months before admission a febrile illness developed which was called "pneumonia." This lasted about five weeks. There was gradual improvement thereafter until four weeks before admission, when tender purulent lesions appeared on the gums. This was diagnosed "trench mouth" and treated locally with hydrogen peroxide and arsphenamine. She complained also of feverishness, night sweats and pains in the joints.

She was well developed, somewhat undernourished and obviously both chronically and acutely ill. The face showed deep pigmentation of the skin extending from cheek to cheek over the bridge of the nose in butterfly distribution. This zone showed minute telangiectases. Similar changes were present on both ears and over the manubrium, the back of the neck and the scalp. The hair of the eyebrows was scanty, and there were several areas of alopecia behind each ear. The lips were markedly swollen and covered by reddened vesicular lesions surmounted by yellowish black hemorrhagic crusts. There was similar involvement of the oral and gingival mucous membranes. Bilateral acute conjunctivitis was present. The ocular fundi showed white exudates. The heart was not enlarged. There was a short systolic murmur at the apex. The blood pressure was 125 systolic and 80 diastolic. There were a few crackles in the right lung laterally. The edge of the liver was palpable at the costal margin. The spleen could not be felt.

The hemoglobin level was 58 per cent; the red blood cell count, 3,500,000; the white blood cell count, 4,900, with 81 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The platelet count was 250,000. Examination of the urine revealed a fixation of specific gravity from 1.010 to 1.012 even after concentration. The albumin content varied from 1 to 2 plus. Repeated examinations of the urine showed granular and hyaline casts, occasional red blood cells and white blood cells. The blood urea nitrogen on admission was 24 mg. per hundred cubic centimeters. Blood for the Wassermann test was anticomplementary on two occasions; the Kahn test was negative. Two blood cultures were negative. Smears taken from the oral lesions revealed no spirochetes or fusiform bacilli. The electrocardiogram showed sinus tachycardia and low voltage of the QRS waves.

The patient was febrile throughout her three weeks' stay in the hospital, the temperature going to as high as 105 F. The oral lesions were treated vigorously, without much improvement. They were thought to be independent of the lupus erythematosus, possibly an exudative erythema multiforme secondary to drugs. At the end of the first week signs of pneumonia in the lower lobe of the left lung were ushered in by a chill. Concomitantly there was an exacerbation of the cutaneous eruption. A maculoerythematous efflorescence, in some places slightly vesicular, appeared in the older pigmented areas. The pneumonic signs spread progressively in both lungs. Associated with this pulmonary infection (a pure culture of Staph. aureus was obtained from the sputum), the white blood cell count rose to 14,800 and later to 25,300, with 95 per cent polymorphonuclear leukocytes. The patient became profoundly toxic and finally stuporous. The blood urea nitrogen rose steadily to reach a level of 75 mg. per hundred cubic centimeters before death. Preterminally, signs of pleuritis and pericarditis appeared.

Anatomic Diagnosis.—Disseminated lupus erythematosus; bronchopneumonia; focal organizing pericarditis with small pericardial effusion; acute fibrinous pleuritis; sacral decubitus ulcer.

CASE 5.—The patient was a 32 year old white woman, widowed for two years. Six months before admission she was taken ill with severe pains in the joints and muscles, necessitating almost continuous rest in bed. The temperature was not recorded, though there was malaise. She was advised to go to Florida. There she exposed herself to the sun. Her pains continued. She lost her appetite and lost 12 pounds (5.5 Kg.) in weight. She occasionally vomited. She began to experience dyspnea on exertion. On the last day of her stay in Florida she noticed an erythematous rash in butterfly pattern over the nose and cheeks. Such an eruption had never occurred before, although she had spent a good deal of time at the seashore. During the preceding year she had been in Florida for eight months without untoward effects.

She returned home about ten days before admission with a new complaint: stabbing pains substernally and in both sides of the chest, aggravated by respiration.

Examination revealed an acutely ill young woman. The temperature was 102.2 F.; the pulse rate, 84; the respirations, 20. The skin was deeply sunburnt in the exposed portions. There was also diffuse tenderness of the skin. The face was marred by a purplish eruption involving the nose and cheeks. It spread toward the chin and superciliary areas. There was fine scaling. The V area of the neck was similarly involved. Several fingers showed small purple-red lesions, which did not fade completely on pressure. The cervical, axillary and inguinal lymph nodes were enlarged to almond size.

The eyes were quite myopic. There was bilateral posterior staphyloma. The lungs were normal. The heart was slightly enlarged to the left. There was an apical systolic murmur. The blood pressure was 104 systolic and 50 diastolic. The spleen was not palpable.

The hemoglobin content was 58 per cent; the red blood cell count, 2,900,000; the white blood cell count, 8,300, with 78 per cent neutrophils, 16 per cent lymphocytes, 5 per cent monocytes and 1 per cent plasma cells. The blood platelet count was 22,000. The urine had a specific gravity varying from 1.016 to 1.026 and showed persistent albuminuria (from a trace to 3 plus). Microscopically, there were occasional granular casts and white cells, and on only one examination, rare red blood cells. The sedimentation time of the red blood cells was eighteen minutes. The Wassermann test of the blood was negative. Urea nitrogen was 18 mg., calcium 8.6 mg., phosphorus 3.4 mg., albumin 3.2 Gm. and globulin 3.5 Gm. per hundred cubic centimeters. The electrocardiogram showed low voltage in the QRS complexes. Several blood cultures were negative. Then one showed a growth of Str. haemolyticus in one of several flasks only.

The course was marked by fever, with the temperature ranging to 104 F. Soon after admission a gallop rhythm became audible. On the third hospital day frank signs of consolidation in the lower lobe of the left lung developed. The sputum showed no pneumococci. One week later there were signs of consolidation in the lower lobes of both lungs. Treatment with nicotinic acid brought no improvement in the clinical picture. The course continued steadily downhill. The cutaneous lesion progressed definitely. The scaling eruption of the face and neck became more marked; lesions developed on both elbows. Several large bullae appeared on the back. These went on to superficial necrosis. The patient became disoriented and delirious. She died eighteen days after admission.

Anatomic Diagnosis.—Disseminated lupus erythematosus; bilateral bronchopneumonia; acute purulent pleuritis on the right (Str. haemolyticus); acute fibrinous pleuritis on the left; focal organizing pericarditis; focal fibrous perisplenitis and

perihepatitis; ulcerative esophagitis and proctitis; fatty change of the liver; old primary tuberculous complex in the upper lobe of the left lung.

CASE 6.—A 40 year old Russian-born white housewife had good health up to three years before examination. At that time she first noted edema of the ankles, which gradually increased. Two years before admission she suffered frequent headache and had nocturia and edema of the eyelids. She was told that her urine contained pus, that her blood pressure was elevated and that she had "kidney trouble." Three weeks prior to admission she had sharp pain in both breasts without swelling or redness. A week later she was taken with intense pain in the right upper part of the abdomen. There were nausea and vomiting. Her physician found her temperature 102 F. and her systolic blood pressure over 260 mm. of mercury. She remained in bed, and the abdominal pain gradually subsided. Three days before admission she first experienced high fever, chilly sensations and marked prostration. Two days later a rash appeared over the face. It was recalled that she had exposed herself to the sun for several hours at a time in the past few months. In addition, she had had her hair dyed five weeks before admission. There was no history of previous rheumatic fever or acute glomerulonephritis.

On admission she was acutely ill, febrile and slightly disoriented. The retinal arteries were narrowed. There were a few hemorrhages in one fundus. There were small purpuric spots on the soft palate. Coarse rales were heard in both sides of the chest and a blowing systolic murmur over the precordium. The heart was not large. The blood pressure was 140 systolic and 100 diastolic. The abdomen was soft. The liver extended 2 fingerbreadths below the margin of the ribs. The spleen was not felt. Distributed over the nose and cheeks in a butterfly pattern and over the eyelids, superciliary ridges, forehead and upper lip was a slightly scaly maculoerythematous eruption. The dermatologic consultant considered this "suggestive of subacute disseminated lupus erythematosus."

The hemoglobin content was 43 per cent; the red blood cell count, 2,240,000; the white blood cell count, 5,500, with 83 per cent polymorphonuclear leukocytes. The sedimentation time was sixteen minutes for 18 mm. The tourniquet test was slightly positive. The Wassermann test of the blood was negative. The urine repeatedly showed albumin (2 plus), red cells, white cells and casts. The blood urea nitrogen was 35 mg., sugar 110 mg., calcium 7.5 mg., phosphorus 4.5 mg., total protein 4.3 Gm., albumin 1.3 Gm. and globulin 3.9 Gm. per hundred cubic centimeters. Blood cultures were negative. The electrocardiogram showed no abnormality. In a concentration test the maximum specific gravity of the urine was 1.014.

The patient lived for four weeks, during which time she was never afebrile. Her temperature fluctuated between 100 and 105 F. The lungs were clear. She vomited frequently and complained of epigastric pain. For a period of several days there was also persistent severe substernal pain. At times she was delirious. The blood urea nitrogen two weeks after admission was only 29 mg. per hundred cubic centimeters, in spite of the fixed specific gravity of the urine. Only terminally was the blood urea nitrogen 72 mg. per hundred cubic centimeters. She died in profound toxemia.

Anatomic Diagnosis.—Disseminated lupus erythematosus; focal bronchopneumonia; parenchymatous degeneration of the heart; hypertrophy (slight) and dilatation (moderate) of both ventricles; focal fibrinous pericarditis and pleuritis; fibrinous perisplenitis; fatty changes of the liver; patent ductus arteriosus; fibromyoma of the uterus.

CASE 7.—The patient was a 23 year old white woman, a fur worker. Five months prior to admission she had two paronychiae complicated by suppuration of the epitrochlear and axillary lymph nodes. After surgical drainage (Staph. aureus cultured) she soon recovered. At that time the urine showed albumin (3 plus), a few white blood cells, leukocyte casts and some red blood cells. The Wassermann test was made on the blood twice; the first reaction was 4 plus. One week later she became ill with chills, fever and cough. She was hospitalized elsewhere. A molar tooth was extracted for "alveolar abscess." The symptoms persisted for several weeks, and signs of pleuritis and pneumonia in the right lung developed. The leukocyte count was 18,200. The urine showed albumin. Clear fluid was removed from the right side of the chest. The Wassermann test of the blood was negative; the Kahn reaction was 2 plus. Showers of conjunctival petechiae were observed. After three weeks the patient entered the Mount Sinai Hospital.

The temperature was 103.2 F.; the pulse rate, 140. There were marked dyspnea and orthopnea. The skin over the bridge of the nose was slightly thickened and pigmented, and this area together with the malar eminences showed a flush in butterfly pattern. There were signs of pneumonia in the lower lobe of the right lung. The heart was slightly enlarged to the left. There was a systolic murmur over the pulmonic area and a soft diastolic murmur over the apex. The blood pressure was 135 systolic and 60 diastolic. Petechiae were present on the neck. The superficial lymph nodes were not enlarged. The spleen was not palpable.

The hemoglobin content was 30 per cent; the red blood cell count, 2,240,000; the white blood cell count, 16,200, with 81 per cent neutrophilic leukocytes. The urine had a specific gravity of 1.020 and showed a trace of albumin, hyaline and granular casts, a few red blood cells and white blood cells. The Wassermann test of the blood was negative. The blood urea nitrogen was 27 mg., total protein 5 Gm., albumin 2.2 Gm. and globulin 2.9 Gm. per hundred cubic centimeters.

The patient had a septic temperature curve, reaching 104 F. She had a single convulsive seizure, observed only by a nurse. Within a week general edema developed. Pneumonia migrated to the lower lobe of the left lung. The heart outline at one time increased in size, and a palpable rub appeared over the midsternum. The liver was tender and had increased in size. Scattered purpuric spots appeared. Clubbing of the fingers was noted.

Repeated blood cultures were negative. Electrocardiograms showed low voltage of the QRS complexes and minor changes suggestive of myocardial damage. Fluoroscopic examination of the chest revealed right and left cardiac enlargement and changes suggestive of pericardial effusion. A urinary concentration test done after marked edema had developed showed a maximum specific gravity of 1.012.

Dermatologic consultants did not see the patient until after the butterfly lesion of the face had disappeared. During short afebrile periods there was slight leukopenia—leukocyte count, 5,900. During her stay of almost four months in the hospital the patient was given numerous transfusions, frequently in such small amounts as 125 cc. because of the poor cardiac reserve. Decubitus ulcers and suppurative femoral lymphadenitis developed. The latter was drained with a good result. The patient complained bitterly of precordial, epigastric or abdominal pain. She was dyspneic and cyanotic much of the time. Renal insufficiency gradually developed, keeping pace with the accumulation of fluid. The blood proteins fell to 4.5 Gm. per hundred cubic centimeters, with albumin 1.8 Gm. and

globulin 2.7 Gm. There was a great deal of vomiting. Hypertension also appeared in the last weeks. One week before death the blood pressure was 150 systolic and 120 diastolic. The blood urea nitrogen terminally was 110 mg. per hundred cubic centimeters. The patient died in uremia.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving all valves and the right auricle and both ventricles; chronic adhesive pericarditis and pleuritis; chronic perisplenitis and perihepatitis; anasarca; ascites; bilateral pleural effusion; chronic fibrosing nonsuppurative mediastinitis; hypertrophy of both ventricles; chronic passive congestion of the lungs and liver; partial atelectasis of the lower lobe of the left lung; hemosiderosis of the spleen; congenital aneurysm of the septum membranaceum; thrombosis of the uterine veins.

Case 8.—The patient was a white girl 7 years of age. Her mother had been treated for seventeen years for lupus erythematosus of the nose. The child herself had had whooping cough, measles and chickenpox. For the past three years she had complained of pains in various joints. Six weeks before admission, following a day at the beach, she had a moderately severe sunburn of the face, shoulders and arms. The next week she again exposed herself to the sun and acquired an even more severe burn. One week later a red eruption appeared in butterfly pattern over the nose and cheeks. It spread to the chest and shoulders. A week before admission she complained of pains in the fingers, knees and ankles. The mother also noted red patches on the oral mucous membrane. She became febrile. Her appetite was lost, and she vomited several times in the last few days before admission to the hospital on August 20.

The child was well developed and well nourished. She complained of pains in both hands. The eruption of acute disseminated lupus erythematosus was present on the forehead, nose, cheeks, ears, arms and right hand. Over the upper anterior part of the chest a few lesions conformed to the neck line of a bathing suit. At the right angle of the mouth there was a red ulcerated lesion. The buccal mucous membranes were studded with many small red raised lesions. The lymph nodes were not enlarged. The heart was normal. The blood pressure was 106 systolic and 70 diastolic. The lungs were clear. The spleen was felt 1 fingerbreadth below the costal margin.

The hemoglobin content was 77 per cent; the red blood cell count, 5,100,000; the white blood cell count, 10,000, with 69 per cent polymorphonuclear leukocytes. The urine was well concentrated; the albumin in the urine varied from 1 to 3 plus. A few casts, red blood cells and white blood cells were present at all times. The blood urea nitrogen was 11 mg., albumin 3.4 Gm. and globulin 2.7 Gm. per hundred cubic centimeters. Schick and tuberculin tests were negative. An electrocardiogram showed sinus tachycardia (rate, 135), a high voltage of QRS, a high and pointed T_1 and a deeply inverted T_3.

During the entire course in the hospital there was low grade fever (from 100.8 to 101.0 F.). On September 16 a tooth was extracted. Following this, there was an elevation of temperature to 102 F., and the general condition became temporarily worse. Blood cultures were negative. In the first month the hemoglobin fell to 60 per cent, the red blood cell count to 2,700,000 and the white blood cell count to 5,200. The cutaneous lesions underwent regressive changes and exacerbations. Clubbing of the fingers and toes developed under observation. Hemorrhagic lesions appeared at the bases of the finger and toe nails. In January bilateral otitis media supervened, with a rise in temperature to 102 F. Blood

cultures were again negative. After myringotomy there was improvement. Shortly thereafter the face became puffy. Toward the end of February a large tender node appeared in the right groin. This was accompanied by a daily rise of temperature to between 103.5 and 106.8 F. Signs of pleuritis and pneumonia followed. Death was preceded by two general seizures. The total duration of illness was eight months.

Anatomic Diagnosis.—Disseminated lupus erythematosus; suppurative bronchopneumonia on the right, with acute fibrinous pleuritis; bronchopneumonia of the lower lobe of the left lung; chronic fibrous perisplenitis; acute fibrinous pelvic peritonitis; focal necrosis of the liver and lymph nodes; hypertrophy of the left ventricle.

Case 9.—A 35 year old white woman had as her chief complaints on admission to the hospital loss of weight, dysphagia and anorexia, fever, pains in the joints and weakness. Until four years prior to hospitalization her health had been good. At that time she experienced pain and tenderness in her joints. From then on she had migratory attacks of arthritis without swelling of the joints. Two months before admission she was placed on an orange juice diet at a physical culture sanatorium. Her weight fell from 108 to 88 pounds (49 to 40 Kg.). She contracted "pneumonia." This lasted about two weeks. Subsequently, however, up to the time of admission to the hospital, she was rarely free of fever. She became extremely weak. Just prior to hospitalization she showed a distaste for food because swallowing was very painful. In addition, she had become dyspneic.

She was extremely thin and obviously chronically ill. The temperature was 103.6 F.; the pulse rate, 122; the respirations, 32. The skin was clear. There were vague signs in both lungs inferiorly. The heart seemed slightly enlarged to the left. There was a short presystolic murmur. The blood pressure was 90 systolic and 50 diastolic. The abdomen was slightly tender in the upper right quadrant and in the lower quadrants. The spleen was not palpable. There were no joint changes.

The hemoglobin content was 55 per cent; the white blood cell count, 6,000, with neutrophilic leukocytes 86 per cent and lymphocytes 14 per cent. The urine had a specific gravity of 1.020 and contained albumin (3 plus), occasional red blood cells and leukocytes.

The temperature curve was septic in type. The blood culture was negative. The patient complained of nausea and vomited repeatedly, so that nourishment was difficult. Small ulcerations appeared in both corneas. These tended to heal with local treatment. There were attacks of severe pain in the right lower quadrant of the abdomen. A few days after admission she began to cough. Signs of pneumonia were found in the lower lobe of the left lung. On roentgen examination, small pleural effusions were also seen in both sides of the chest. The heart was observed to be enlarged to the right as well as to the left. At the end of the second week in the hospital a maculoerythematous eruption came out over both malar prominences. The lesion was superficial, nonindurated and cherry red. It spread rapidly over almost the entire face, sparing the circumoral region, the center of the chin and the region above the eyebrows. Later, however, even these areas became involved. In addition, the lips, gums and hard palate showed shallow ulcerations. During this time the pneumonia in the lower lobe of the left lung showed evidence of resolution. The vomiting and dysphagia persisted, however. No intrinsic lesions of the esophagus were discoverable by roentgen examination. The corneas became dry and showed superficial fluorescein-

stainable defects. The conjunctivas were thick and red. The patient deteriorated steadily. Tachycardia and increasing dyspnea were noted. Pain under the costal arch suggested pericarditis. Finally, small lentil to pea-sized purple hemorrhagic areas appeared over the left ear lobe, the sacrum, the buttock, the left heel and the fifth terminal phalanx of the left hand. These were thought to be due to capillary thromboses. At this time the temperature had been fluctuating between 100 and 105 F. The patient continued to cough without raising much sputum. She became irrational at times. Death occurred almost two months after she entered the hospital.

Anatomic Diagnosis.—Disseminated lupus erythematosus; chronic fibrous pericarditis, pleuritis, perisplenitis and perihepatitis; chronic fibrosing nonsuppurative mediastinitis; bilateral bronchopneumonia and partial pulmonary atelectasis; pericardial effusion; hypertrophy of the right ventricle; fatty change of the liver; generalized lymphadenopathy.

Case 10.—An 18 year old white woman was well until one year before admission, when she experienced migrating pain and swelling in various joints. She became progressively weak. Two and one-half months before admission, following a moderately severe sunburn, a persistent erythema appeared on the face. For one month there was anorexia, and for three weeks, moderate fever, night sweats and exacerbation of the pains in the joints. One week before coming to the hospital she experienced transient precordial pain.

Examination revealed a well developed, well nourished white girl. The temperature was 101.2 F.; the pulse rate, 100; the respirations, 24. In butterfly distribution over the nose and cheeks were slightly scaly raised confluent erythematous lesions. Similar lesions were present over the eyebrows and on the upper part of the back and over the left shoulder. Slightly tender enlarged lymph nodes were present in the neck, axillas and groins. The heart was not enlarged. There was a systolic murmur in the pulmonic and aortic areas. The blood pressure was 112 systolic and 58 diastolic. The edge of the liver was just palpable and moderately tender. There was slight thickening of the proximal phalangeal joints of both hands. The left shoulder was tender and painful on motion.

The hemoglobin value was 57 per cent; the red blood cell count, 3,700,000; the white blood cell count, 4,500, with 57 per cent neutrophils, 3 per cent eosinophils, 1 per cent basophils, 4 per cent neutrophilic myelocytes, 26 per cent small lymphocytes, 2 per cent large lymphocytes and 7 per cent monocytes. The blood platelet count was 130,000. The sedimentation time was fifty-five minutes. The urine had a specific gravity of 1.020 and showed albumin (2 plus), occasional red blood cells and white cells. The Wassermann test of the blood was negative. The blood urea nitrogen was 34 mg., total protein 6.5 Gm., albumin 3.7 Gm. and globulin 2.8 Gm. per hundred cubic centimeters. The electrocardiogram showed left ventricular preponderance.

The course from the beginning was progressively downhill. There were pains in the joints and low grade fever. The sedimentation time of the red blood cells became more rapid. There was progressive anemia in spite of blood transfusions. The eruption on the face became more florid and spread to the chest. Erythematous lesions appeared on the hard palate. Nausea and vomiting were persistent. Signs of pneumonia appeared in the lower lobes of both lungs and fluid collected in both sides of the chest. Pitting edema developed in the legs and back. Blood cultures were negative. The spleen became palpable.

In the sixth week a pericardial friction rub was heard. Dyspnea became marked and was somewhat relieved by aspiration of fluid from the chest, which was sterile though cloudy. The blood pressure rose to 149 systolic and 94 diastolic. Albuminuria and hematuria persisted. After two months, in addition to the accumulation of pleural fluid, ascites occurred. Diffuse pruritus developed. Purpuric hemorrhages appeared in the skin. The patient became irritable and garrulous. A left facial weakness and a left Babinski reflex were present for a short period. The blood urea nitrogen at one time was 55 mg. per hundred cubic centimeters. Neuroretinitis with a fundal hemorrhage was observed. At the time of death, three months after admission, the patient exhibited profound toxemia. The blood urea nitrogen four days before death was only 37 mg. per hundred cubic centimeters. Throughout the febrile course blood cultures were persistently negative.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving the mitral, aortic and pulmonic valves and the left ventricle; moderate hypertrophy and dilatation of the left side of the heart; chronic organizing bilateral pleuritis; chronic perisplenitis and perihepatitis; chronic glomerulonephritis; bilateral hydrothorax and ascites; peripheral edema; partial atelectasis of the lower lobes of the lungs; splenomegaly (weight of spleen, 450 Gm.); generalized lymphadenopathy; pulmonary infarct; fatty change of the liver; petechial hemorrhages of serous membranes; adenoma of the liver; stercoral ulcerations of the sigmoid colon; old calcified primary tuberculous complex in the upper lobe of the left lung.

Case 11.—A 24 year old Italian-American factory girl enjoyed good health until three months prior to admission. At that time she became weak and complained of vague abdominal pain. A red eruption appeared over the face, hands and feet. The involved areas became somewhat swollen. Pain in both knee joints developed. This symptom soon subsided, but the cutaneous lesions remained, and those on the face spread over the cheeks, chin, nose, forehead and ears. The lesions on the hands became vesicular. The patient became progressively weaker, lost her appetite and began to lose weight. On the day prior to admission she had a shaking chill followed by a high fever and cough.

She was well developed and well nourished but appeared acutely ill, irrational and disoriented. The temperature was 103.2 F.; the pulse rate, 140; the respirations, 28. Over the entire face except the circumoral region, irregularly extending above the eyebrows, behind the ears and just below the rami of the jaws, were slightly pigmented scaling confluent erythematous macules with some tendency to vesicle and even pustule formation. Similar lesions were present on the volar aspects of the finger tips and on the dorsal surfaces of the fingers. Telangiectases were present. On the front of the legs and thighs were dark red macules with a purpuric tendency and telangiectasia. The hard palate showed confluent erythematous maculopapular lesions. The ocular fundi were normal. The heart was slightly enlarged to the left. There was a protodiastolic gallop rhythm. The blood pressure was 120 systolic and 90 diastolic. There were dulness at the base of the right lung, diminished breath sounds and fine rales. The spleen was not palpable. Several ulcerated, scaly lesions were present on the labia minora. Small shotty lymph nodes were found in the axillas and groins.

The hemoglobin content was 68 per cent; the red blood cell count, 7,100,000; the white blood cell count, 15,700, with 94 per cent neutrophils, 5 per cent lymphocytes and 1 per cent monocytes. The urine was of specific gravity 1.016, with 2 plus albumin and many white blood cells. The Wassermann test of the blood was

negative. The blood urea nitrogen was 34 mg. per hundred cubic centimeters. A blood culture revealed Pneumococcus type XIX.

The signs in the lower lobe of the right lung developed into those of frank consolidation. The same signs appeared in the lower lobe of the left lung. Dyspnea and cyanosis were extreme in spite of the administration of oxygen and blood transfusion. The patient died three days after admission.

Anatomic Diagnosis.—Disseminated lupus erythematosus; lobar pneumonia involving all lobes except the middle lobe of the right lung; acute fibrinous and fibrous bilateral pleuritis; multiple necroses in spleen and lymph nodes; hemorrhages in the epicardium, bladder, stomach and duodenum.

Case 12.—A 30 year old single white woman, a stenographer, was entirely well until two years before admission, when she noted tingling, numbness and cyanosis of the finger tips on exposure to even slight cold. These symptoms persisted for a year, and then a blotchy erythema developed over the bridge of the nose and malar eminences, associated with swelling of the lips. There were frequent episodes of swelling, redness and pain of the interphalangeal joints of both hands. Transitory remission of these symptoms occurred until four weeks before admission to the hospital, when she undertook an eleven day sea voyage. She was taken violently ill on the first day out with intense hemicrania, fever, severe epigastric pain, nonproductive cough and marked weakness. The eruption on the face became red and angry. Throughout the cruise, she exposed herself to the sun inordinately. The illness persisted. On arriving home, she had pains in the muscles and joints and marked erythema of all exposed areas of the body. The eyes were puffy. She entered the hospital two weeks later.

The patient appeared acutely ill. The temperature was 100 F.; the pulse rate, 80; the respirations, 20. The face, nose and lips were covered by a partially crusted erythematous eruption, which extended back to the ears and up to the hair line. The hands and the volar aspects of the fingers were the site of a bright red erythema, in some places hemorrhagic. There was also a scaly dry erythema over the upper extremities, chest, neck and back. There was a small erythematous lesion on the hard palate. The heart was slightly enlarged to the left. A soft systolic blow was heard at the apex. The blood pressure was 108 systolic and 70 diastolic. The lungs were normal. The spleen was not felt. Soft large lymph nodes were felt in the neck and left axilla.

The hemoglobin content was 70 per cent, and the white blood cell count, 3,400, with 33 per cent neutrophils, 65 per cent lymphocytes and 2 per cent monocytes. The blood platelet count was 130,000. The sedimentation time was twenty minutes. The Wassermann test of the blood was negative. The urine showed good specific gravity; no albumin and only occasional white blood cells were observed. The blood urea nitrogen was 18 mg., calcium 8.2 mg., phosphorus 4.0 mg., albumin 3.6 Gm. and globulin 3.0 Gm. per hundred cubic centimeters.

The patient continued to have fever, the temperature rising as high as 104 F. She was drowsy and complained of abdominal pain. The cutaneous lesions became more intense and spread more widely. Over the finger tips, they became bullous. Albumin appeared in the urine. A blood culture taken on the third day showed Str. viridans in only a single flask. A subsequent blood culture was negative. However, after two and one-half weeks she had a shaking chill, and the temperature rose to 105.6 F. Culture of the blood at this time revealed Str. haemolyticus in large numbers. No focus was found in the upper respiratory tract. She died three weeks after admission.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving the tricuspid, mitral and aortic valves; chronic rheumatic mitral valvulitis; retroperitoneal abscess; focal fibrous pericarditis; bilateral bronchopneumonia; focal fibrinous pleuritis; fatty change of the heart and liver.

CASE 13.—This was the second admission of a 22 year old white woman, who was well until four years before coming to the hospital for the first time. This initial phase of her illness began with pain, redness and slight swelling of the finger and knee joints. Also, she had a reddish eruption over the nose and cheeks in butterfly distribution. A course of ten intravenous injections of a gold salt was given. The symptoms of disease of the joints and the rash resolved within three months. She was well until about sixteen months before the first admission, when the symptoms of involvement of the joints and the rash recurred. She was told that her lymph nodes were enlarged. Large doses of gold salts were given intravenously. Three weeks before the first admission, following exposure to the sun, an eruption on the arms, chest, back and thighs, similar to that on the face, appeared. At the time of admission there was an elevation of the temperature to 100 F. The blood pressure was 115 systolic and 75 diastolic. The hemoglobin content was 75 per cent, and the white blood cell count was 4,400 with 61 per cent neutrophilic leukocytes. The urine showed occasional red blood cells but no albumin. The right antrum was irrigated and pus evacuated, yielding Staph. aureus and Pneumococcus type XXIX on culture. After three weeks in the hospital she improved; the skin lesions faded considerably.

She felt well for five months, until one month prior to the second admission. At that time the rash was light brown and not extensive. Without warning, she suddenly became ill. There were nausea and vomiting. She became feverish. The facial lesions became red, and new scaly reddish lesions appeared at the base of the finger nails. She lost appetite, and diffuse abdominal pain and pain on the left side of the chest developed. There were daily episodes of epistaxis, then pain and tenderness in many of the joints, then cough and severe occipital headache. At the time of admission to the hospital, the cutaneous lesions on the face and fingers had faded somewhat.

She appeared well developed and well nourished but subacutely ill. The temperature was 100 F.; the pulse rate, 84, the respirations, 20. The face was pale and puffy, and there were scaly raised reddish brown lesions over the bridge of the nose and cheeks, eyelids, eyebrows, chin, lips and left ear lobe. There were similar lesions over the knuckles, finger tips, toes and soles. There were also petechial spots over the knuckles. The suboccipital, axillary and inguinal lymph nodes were enlarged. The right ocular fundus showed a flame-shaped hemorrhage. Petechiae were present on the soft palate. The heart was slightly enlarged. There was a soft systolic murmur heard over the entire precordium. The blood pressure was 120 systolic and 70 diastolic. The lungs were clear. The spleen was not palpable.

The hemoglobin content was 49 per cent; the red blood cell count, 2,500,000; the white blood cell count, 6,300, with 63 per cent neutrophils, 2 per cent myelocytes, 30 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils and 1 per cent plasma cells. The bleeding time was two minutes, the clotting time four minutes and clot retraction good in four and one-half hours. Blood platelets numbered 110,000 per cubic millimeter. The tourniquet test was slightly positive in five minutes. The urine showed albumin (3 plus), occasional red blood cells and white blood cells, but no casts. The maximum concentration of the urine

was to specific gravity 1.012. The Wassermann test of the blood was negative. The blood urea nitrogen was 27 mg., calcium 8.6 mg., phosphorus 4.8 mg., total protein 5.1 Gm., albumin 2.8 Gm. and globulin 2.3 Gm. per hundred cubic centimeters. A blood culture was negative. The blood sedimentation time was fifteen minutes. No porphyrins were found in the urine. The electrocardiogram showed a P-R interval of 0.22 second, a QRS of low voltage and a diphasic T_1.

For almost a month the temperature remained within normal limits. Nevertheless pains in the joints persisted, and she had daily nosebleeds. Albumin, red and white blood cells, and casts were found in the urine constantly. Then the temperature mounted. The pains in the joints became more severe, and the cutaneous lesions blossomed and spread. Pleuritis and effusion developed in the left side of the chest. There were nausea and vomiting. Symmetric erythematous lesions resembling erythema multiforme appeared on both arms. Marked pitting edema developed over the back. Red, tender edematous areas appeared in the subcutaneous tissues of the buttocks, abdominal wall and thighs. These suggested dermatomyositis. The hemoglobin dropped as low as 35 per cent. Blood transfusions were given. Fever persisted, and the patient became quite dyspneic. There was profound toxemia. The patient died two and one-half months after admission.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving the mitral valve, with superimposed bacterial endocarditis (gram-positive cocci); chronic rheumatic valvulitis, mitral and aortic; diffuse subacute glomerulonephritis; bronchopneumonia on the right; bilateral acute fibrinous pleuritis with effusion; atelectasis of the left lung; splenomegaly; infarct of the spleen; generalized lymphadenopathy; calcified tuberculous tracheobronchial lymph node.

CASE 14.—The patient was a 26 year old unmarried white woman, a stenographer. Seven years before admission she had had pains in the shoulders, wrists, fingers and knees, lasting several weeks. Four years later an erythematous rash occurred over the nose, cheeks and ears. This was diagnosed as lupus erythematosus. She was given gold sodium thiosulfate intravenously and a bismuth compound intramuscularly. The condition became aggravated. In the course of a year the lesions disappeared without further treatment. One year and a half before admission the patient was confined to bed with left femoral phlebitis subsequent to abrasion of the knee. She was febrile. The hemoglobin level was 60 per cent; the urine was normal. Six months before admission she came to the outpatient department with a "butterfly" erythematous eruption of the face. The heart was enlarged to the right; the blood pressure was 120 systolic and 75 diastolic; there were bilateral pleural adhesions; the hemoglobin content was 70 per cent and the white blood cell count 6,600; the urine showed a trace of albumin. In spite of local treatment of the facial eruption and intramuscular injection of a bismuth compound followed by intravenous injections of a gold salt, the facial eruption progressed. Six weeks before admission edema of the ankles appeared and subsequently dyspnea on exertion. On the day before admission an examination of the urine revealed albumin (4 plus), many casts and white blood cells and a few red blood cells.

On examination the patient, except for moderate anemia, did not appear ill. The temperature was 99 F.; the pulse rate, 88; the respirations, 20. There was a dark red confluent erythematous eruption extending over the dorsum of the nose to both malar regions and showing areas of scaling and atrophy. Similar

lesions were present at the nares, at the inner canthus of the right eye, over the left eyebrow and on the upper lip. There were fleshy lymph nodes in the posterior cervical region and bean-sized nodes in both axillas. The tonsils were absent. The ocular fundi showed only congenital retinal pigmentation. The heart was slightly enlarged. There was a systolic murmur over the entire precordium, roughened and scratchy at the base. A systolic thrill was present over the fourth left interspace. The blood pressure was 130 systolic and 72 diastolic. The lungs were clear. The abdomen was normal. There was pitting edema of both legs up to the knees, more marked on the left side.

The hemoglobin content was 60 per cent; the red blood cell count, 3,840,000; the white blood cell count, 8,600, with 80 per cent neutrophilic leukocytes, 16 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes. The platelet count was 120,000. The sedimentation time was eighteen minutes. The Wassermann test of the blood was negative. Urine could be concentrated up to specific gravity 1.022. There was marked albuminuria, the albumin averaging 3 to 4 Gm. in twenty-four hours; there were occasional to numerous white cells and a rare cast but no red blood cells. Blood urea nitrogen was 14 mg., total protein 5.4 Gm., albumin 3.0 Gm. and globulin 2.4 Gm. per hundred cubic centimeters. No hematoporphyrin was found in the urine. Roentgenograms disclosed enlargement of the left auricle, pulmonary conus and right side of the heart and congestion of the lungs.

The edema of the ankles disappeared in a month. Nevertheless, although the patient was afebrile, the sedimentation rate continued to be rapid, and the anemia became progressively more marked (hemoglobin content, 45 per cent).

The electrocardiogram showed low voltage of the QRS complex. First a phlebitis of the right brachial vein developed (following intravenous therapy) and then a deep phlebitis in the right calf. One month after admission the patient was taken with a sore throat and pain in the wrists and elbows. There was fever. The facial lesions, however, appeared to have subsided somewhat. The albuminuria remained unchanged. Two days after the infection of the upper respiratory tract the temperature suddenly rose to 104 F., the glands on both sides of the neck became enlarged and a patch of exudate was seen on a residual tab of tonsillar tissue. The temperature became septic in character, cyanosis was quite marked, and there was air hunger. The liver came down to the umbilicus. The lungs were clear, and the heart was unchanged. The patient went into peripheral collapse and died on the fourth day after the onset of the fever, apparently in respiratory failure. A blood culture made on the day before death revealed Str. viridans. This was taken to be a preagonal invasion of the blood stream.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis of the tricuspid valve and right ventricle with superimposed acute bacterial endocarditis (Str. viridans); chronic adhesive pericarditis and bilateral pleuritis; chronic perisplenitis and perihepatitis; multiple organizing emboli of the right and left pulmonary arteries with an infarct in the upper lobe of the right lung; an organized thrombus of the left common iliac and left femoral veins; recent thrombosis of the right common iliac vein; acute passive congestion of the liver; lymphadenopathy involving para-aortic, retroperitoneal and inguinal nodes; chronic endocervicitis.

Case 15.—A 12 year old white girl suffered severe sunburn during the summer a year before admission. Several months later she had pain and swelling of the joints of the upper and lower extremities. This was followed by a rash beginning

on the face and spreading over the entire body, accompanied by fever up to 104 F., prostration, weakness and anorexia. She entered another hospital, where blood transfusions were given. In addition, twenty injections of pentnucleotide were administered. The symptoms abated, and the eruption disappeared almost entirely. She remained well until three months before admission, when the eruption recurred on the face. There again were fever, prostration and anorexia. Pains in the joints were also present. The eruption began to fade two months later, but the other symptoms continued, and dyspnea and precordial pain supervened. For three weeks before admission she had a cough with expectoration.

On admission she was pallid and appeared chronically ill. Over the bridge of the nose and extending onto the cheeks in butterfly pattern was a scaly flat erythematous eruption. Similar lesions were present on the upper lip, chin, back and forearms. The lower part of the abdomen was covered by a scaly brownish eruption. There were bluish red spots on the volar aspects of the fingers. Lesions were also present on the lower extremities. There was a small ragged necrotic ulcer on the tongue. Purpuric spots were present on the hard palate. The heart was somewhat enlarged. There was a regular gallop rhythm. There was a harsh to and fro rub and thrill at the pulmonic area. A systolic murmur was heard at the apex. The blood pressure was 86 systolic and 50 diastolic. Flatness, absence of breath sounds and fremitus were found at the base of the lower lobe of the left lung posteriorly. The spleen was not palpable. The knees were stiff, and there was generalized bony tenderness.

The hemoglobin content was 60 per cent; the white blood cell count was 6,300, with 68 per cent polymorphonuclear neutrophils. The Wassermann reaction of the blood was 2 plus.

The temperature gradually rose. The respiratory rate increased. The cough became more frequent, and pain was felt in the left side of the chest on respiration. Signs of bronchopneumonia as well as of fluid were found there. The patient vomited several times. She had a convulsion on the day before death. She died after two and one-half days in the hospital.

Anatomic Diagnosis.—Disseminated lupus erythematosus; acute fibrinous and organizing pericarditis; bronchopneumonia of the lower lobe of the right lung; fibrinous perisplenitis; chronic fibrous perihepatitis; chronic passive congestion of the lungs.

CASE 16.—The patient was a 33 year old married white woman. She had had diphtheria in childhood, pneumonia at the age of 18 and pleurisy three years later. There was no history of rheumatic fever. For many years she had had a chronic cough with expectoration of small amounts of sputum. Her present illness began eight months before admission, when the cough increased, and she raised foul yellow sputum. There were occasional fever, hoarseness and sore throat. Six months later she had severe pain in both axillas, aggravated by respiration. Subsequently she spent a week at the seashore. Following this, an eruption developed on the neck, upper part of the chest and back. She became dyspneic and weak. She then went to a private sanatorium in the mountains, where her general condition became worse. It was decided that she had bronchiectasis rather than tuberculosis. Tubercle bacilli were never found in the sputum. Two weeks before admission she had blood-streaked sputum and even produced half a glassful of bright red blood. There also developed painful ulcerations of the lips and buccal mucous membrane. While she was at the sanatorium,

her temperature rose to 102 or 103 F. daily. New cardiac murmurs appeared which had not been heard before. A single blood culture was negative. There were no pains in the joints.

The patient was profoundly ill. The temperature was 102 F.; the pulse rate, 130; the respirations, 32. There was an eruption, essentially erythematous but with a marked bluish hue, on the nose, upper lip, chin and chest. There was some superficial crusting. On the plantar surfaces of several toes and on the raised areas of the palms and fingers, small nontender erythematous maculopapules were observed. The oral mucous membranes showed scattered erythematous lesions. The mucous membranes of the lips were covered by hemorrhagic crusts. There were rales, whistles and crackles in both lungs, and the breath sounds were diminished, particularly in the left axilla, where marked dulness was also present. The heart was enlarged. There was a loud rough systolic murmur heard best to the left of the lower end of the sternum. The blood pressure was 130 systolic and 80 diastolic. There was a tender ballotable mass in the right side of the abdomen (tongue of liver). The spleen was not plapable. The fingers showed slight clubbing.

The hemoglobin content was 70 per cent; the white blood cell count, 8,000, with 86 per cent neutrophilic leukocytes, 12 per cent lymphocytes and 2 per cent myelocytes. The urine showed albumin (1 to 2 plus), numerous granular and hyaline casts, rare red blood cells and occasional white blood cells; the specific gravity was normal. The Wassermann test of the blood was negative. Blood urea nitrogen was 16 mg. per hundred cubic centimeters. An electrocardiogram showed sinus tachycardia, right axis deviation, low QRS complexes and T waves. Roentgen examination of the chest showed bronchiectasis in the upper lobe of the left lung and unresolved pneumonia at the base of the right lung. The enlargement of the heart suggested a mitral lesion. The sputum contained no acid-fast bacilli.

The temperature fluctuated from 100 to 102.6 F. There was cyanosis. Death occurred rather suddenly on the fifth hospital day.

Anatomic Diagnosis.—Disseminated lupus erythematosus; atypical verrucous endocarditis involving all valves and the right and left ventricles; chronic rheumatic mitral, aortic and tricuspid valvulitis; hypertrophy and dilatation of all chambers of the heart; acute fibrinous and organizing pericarditis; diffuse cylindric bronchiectasis; bronchopneumonia of the lower lobe of the right lung; acute fibrinous and fibrous pleuritis; chronic passive congestion of the lungs and abdominal viscera; chronic perisplenitis; ascites and hydrothorax on the left.

CASE 17.—A 37 year old white housewife four months before admission experienced a rather sudden onset of pain and burning in the interphalangeal joints of both hands. Five weeks before admission she exposed herself to strong sunlight during an entire day. This was followed by the usual sunburn of the face and exposed parts of the chest. After this subsided, an eruption appeared on the chest, and five weeks later, on the face. Two weeks before admission to the hospital, pain, redness and swelling of the knees, toes and temporomandibular joints developed. These pains were not relieved by salicylates. She was not aware of fever, although she had had shaking chills following an intravenous injection given by her family physician.

The patient when examined was well developed and well nourished but appeared chronically ill. She was suffering from pains in many joints. The temperature was 102.4 F.; the pulse rate, 100; the respirations, 24. There was erythema with

telangiectasia over the upper part of the chest. The axillary lymph nodes were pea sized and the number of palpable ones larger than usual. The heart and lungs were normal. The blood pressure was 120 systolic and 80 diastolic. The spleen was not palpable. There were pain on motion, tenderness of the shoulders, wrists, hips, knees and ankles and spindle deformity of all fingers with motion limited by pain. The joints were neither red nor hot.

The hemoglobin content was 78 per cent; the red blood cell count, 3,950,000; the white blood cell count, 15,800, with 62 per cent neutrophils, 33 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The sedimentation time was twenty-seven minutes.

The urine had good specific gravity and showed albumin (from a trace to 2 plus), rare to occasional red blood cells, occasional white blood cells and casts. The Wassermann test of the blood was negative. The blood urea nitrogen was 14 mg. per hundred cubic centimeters.

The temperature ranged from 101 to 104 F. After five days a butterfly erythematous eruption, characteristic of acute lupus erythematosus, appeared over the bridge of the nose and cheeks. The older eruption on the chest became florid. Thereafter the elevation of temperature persisted at a high level. Punctate red areas appeared on the soft palate, became large and ulcerated. A blood culture was negative. The patient became apathetic and incontinent. The blood urea nitrogen rose to 57 mg. per hundred cubic centimeters. Purpuric spots appeared on the dorsum of the left hand. A short apical systolic murmur became apparent. Stiffness of the neck, a bilateral Kernig sign and photophobia developed in the fourth week. She became semistuporous. The spinal fluid, however, was normal; its pressure, not increased. On the day before death the blood urea nitrogen was 35 mg. per hundred cubic centimeters. The patient died in stupor.

Anatomic Diagnosis.—Disseminated lupus erythematosus; acute ulcerations of the soft palate; acute purulent bronchitis; atelectasis in the lower lobe of the left lung; necrosis of retroperitoneal lymph nodes.

Case 18.—The patient was a white woman 23 years of age. Her past history is irrelative except that she is said to have had rheumatic endocarditis at the age of 10. Six months before admission there appeared, following "grip," a red blotchy eruption over the face and then over the entire body. This cleared up completely after six weeks. She then began to note stiffness of all the joints. These were rarely painful and never inflamed. She remained in bed for two weeks because of inability in getting about. She was well for six weeks thereafter, until the right knee became painful and stiff. Two weeks before admission a temperature as high as 103 F. was noted and a new rash consisting of dusky red irregular blotches appeared over the entire body. The lesions of the cheeks fused over the bridge of the nose. Anorexia and weakness had been present for three months, and she had lost 10 pounds (4.5 Kg.) in about five weeks. A few days before admission a red spot, disappearing on pressure, had appeared on the right thumb.

Examination revealed a pallid but well nourished young woman. The temperature was 103.8 F.; the pulse rate, 128; the respirations, 28. Over the bridge of the nose and adjacent areas of the face was a patchy bluish erythematous eruption without scaling or atrophy. Similar lesions were present on the forehead, temples, cheeks, neck, breast, chest and arms. On the abdomen the lesions were larger and paler. Over the elbows they were more erythematous. The lungs were normal. The heart was not enlarged. A systolic murmur was heard to the

left of the sternum. The blood pressure was 98 systolic and 70 diastolic. The spleen was not palpable. There were no apparent changes in the joints.

The hemoglobin content was 55 per cent; the red blood cell count, 3,070,000; the white blood cell count, 7,050, with 92 per cent neutrophilic leukocytes, 4 per cent lymphocytes and 4 per cent monocytes. The platelet count was 190,000. The coagulation time was eight minutes; the bleeding time, two minutes. Urinalysis showed: specific gravity 1.018 to 1.020, albumin (3 to 4 plus) on all tests, as well as occasional hyaline and granular casts and red and white blood cells. The Mantoux test with 0.1 mg. of old tuberculin was negative. Blood urea nitrogen was 11 mg., albumin 7.3 Gm. and globulin 1.8 Gm. per hundred cubic centimeters.

During the first week there was a definite increase in the intensity of the eruption on the face, and for the first time lesions appeared over the entire back. The temperature was intermittently high. On the fourth day it rose to 105 F., and signs of bronchopneumonia were noted. The patient vomited persistently. The temperature remained at a high level, and the patient became more and more toxic. Euphoria and difficulty in articulation were present. On the day before death a faint pericardial friction rub was heard. A blood culture taken shortly before the patient died was negative.

Anatomic Diagnosis.—Disseminated lupus erythematosus; bilateral hemorrhagic bronchopneumonia; acute fibrinous pleuritis.

Case 19.—A 17 year old white girl had had pneumonia and diphtheria in childhood but otherwise had been well until the present illness. About five months before admission she noted cutaneous lesions over the bridge of the nose and cheeks. At the same time the glands in the neck were swollen. This lasted for three months. In the month before admission the cutaneous eruption spread to the neck and upper part of the chest. There was a rise in temperature to from 101 to 105 F. She coughed for two weeks. There was persistent vomiting, necessitating rectal feeding. Pain in the right side of the chest was exaggerated by breathing. The throat and tongue became sore. In the ten hours immediately preceding entrance into the hospital she was very short of breath.

At examination the patient was acutely ill and in marked respiratory distress. The temperature was 102.8 F.; the pulse rate, 100; the respirations, 24. There was a diffuse, slightly elevated deep red purpuric eruption in butterfly distribution over the nose and cheeks. There was also involvement of the forehead, clavicular areas, upper part of the back and elbows. Red punctate lesions were seen in the conjunctivas and on the hard palate. Under the left side of the tongue was a shallow ulcer. There were yellowish patches and hard white exudates in the ocular fundi. The heart was not enlarged; a soft systolic murmur was heard at the apex. The blood pressure was 104 systolic and 54 diastolic. There were signs of pneumonia in the lower lobes of both lungs, and a friction rub was present over the middle lobe of the right lung. The spleen was not palpable. There was slight enlargement of the deep cervical lymph nodes.

The hemoglobin level was 53 per cent; the red blood cell count, 2,820,000; the white blood cell count, 28,200, with 92 per cent neutrophils, 7 per cent lymphocytes and 1 per cent monocytes. The blood platelet count was 260,000. Several examinations of the urine showed specific gravity of 1.010 or 1.012, albumin (2 plus), casts, red blood cells and white blood cells. The Wassermann test of the blood was negative. The blood urea nitrogen was 174 mg., calcium 8.3 mg., phosphorus 4.8 mg., albumin 3.3 Gm. and globulin 3.4 Gm. per hundred cubic centimeters.

A roentgenogram of the chest showed an encapsulated pleural effusion in the axillary half of the lower region of the right side of the chest.

A blood culture made on admission showed Staph. aureus. The ulceration on the tongue grew larger, but the facial eruption faded somewhat. Soon generalized muscular twitchings developed. Vomiting was severe. The carbon dioxide-combining power was found to be 75.5 volumes per cent. On the fourth day the breath was uriniferous. Gallop rhythm was heard to the left of the sternum. On the fifth day the blood calcium was 6.8 mg. and the blood phosphorus 5.0 mg. per hundred cubic centimeters. The patient had a convulsion with a carpopedal spasm, which was relieved after intravenous administration of calcium gluconate. A second blood culture showed Pneumococcus type I and atypical colon bacilli. The patient died on the sixth hospital day.

Anatomic Diagnosis.—Disseminated lupus erythematosus; bilateral bronchopneumonia; acute fibrinopurulent pleuritis; chronic fibrous pleuritis on the left; acute hemorrhagic bronchitis; hemosiderosis of the liver.

Case 20.—An 18 year old college girl, white, was admitted with the following complaints: poor appetite, increasing nervousness and irritability for two years; persistent tired feeling and weakness for one year; breathlessness on moderate exertion for four months; transient migrating pains in the wrists, knees and elbows for four months; sudden onset, two weeks before admission, of dizziness, nausea, increase in the severity of pains in the joints and fever, followed in two days by red patches on the face and then a chill. There were also epigastric pain, persistent nausea and vomiting for two weeks. One week before admission there appeared slight swelling of the eyelids and face and a patchy erythema of butterfly distribution over the nose and cheeks. Several days later bleeding of the gums and fissuring of the lips developed. Examination of the urine revealed "blood, albumin, pus, casts and acetone." There was a slightly productive paroxysmal cough. On the day before admission she displayed mental confusion and had auditory hallucinations.

At examination the patient appeared well developed and well nourished. The sensorium was dull. The temperature was 102.8 F.; the pulse rate, 112; the respirations, 22. The nose and adjacent parts of the cheek were covered by a diffuse dark red or purplish red patchy eruption. There was some superficial scaling of the eruption. The palmar surfaces showed lentil-sized faint purplish macules with telangiectasia and incomplete fading on pressure. Scattered over the face and the upper part of the neck were numerous small lesions having the same characteristics as the larger facial lesions. All the lesions showed telangiectasia. The eyelids were slightly puffy. The conjunctivas were reddened. The ocular fundi showed red disks with sharp margins, engorged veins, yellowish white exudates and one small hemorrhage. The lips, palate, buccal and gingival mucous membranes showed hemorrhagic lesions. The heart was slightly enlarged to the left. There was a gallop rhythm with a soft systolic precordial murmur. The blood pressure was 105 systolic and 56 diastolic. The lungs were clear. The spleen was not palpable. Small submandibular and almond-sized axillary lymph nodes were palpable. The superficial and deep reflexes were hypoactive.

The hemoglobin content was 68 per cent; the red blood cell count was 4,500,000; the white blood cell count was 6,800 on admission and 2,300 two days later, with neutrophilic leukocytes 88 per cent and 72 per cent, respectively. The blood platelet count was 190,000. The urine showed albumin (1 plus), a specific gravity of 1.010 to 1.012, occasional red blood cells, white blood cells and casts. The

Wassermann test of the blood was negative; the Kahn test, 1 plus. The blood albumin was 3.6 Gm. and the globulin 2.6 Gm. per hundred cubic centimeters. The blood calcium was 9.8 mg. per hundred cubic centimeters.

After admission to the hospital the patient vomited a great deal and on the second day had a clonic convulsion. The spinal fluid showed 9 lymphocytes but was otherwise normal. The patient became stuporous and delirious and went into coma. Signs of bronchopneumonia appeared in the lower lobes of both lungs. The blood urea nitrogen on the day before death was 34 mg. per hundred cubic centimeters. The temperature ranged between 102 and 104.6 F. A blood culture made on admission was negative, while one made on the day before death revealed Str. viridans. The patient died in coma, three days after admission.

Anatomic Diagnosis.—Disseminated lupus erythematosus; bilateral confluent bronchopneumonia; chronic fibrous pleuritis.

INFLUENCE OF PROMIN, STARCH AND HEPTALDEHYDE ON EXPERIMENTAL LEPROSY IN RATS

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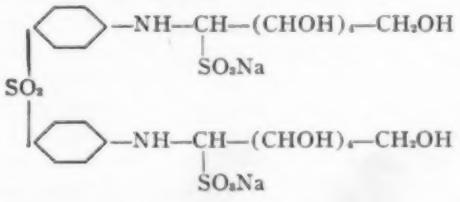
Rat leprosy is so like human leprosy that some even recognize an identity of the two.[1] Cytologically there are many points of similarity and some of difference.[2] In any case the degree of resemblance is sufficiently close to justify the hope that experiments on rat leprosy may yield clues to the treatment of human leprosy. And human leprosy is not unlike human tuberculosis in some respects. If a chemotherapeutic agent could be found for one of the diseases caused by acid-fast bacteria, it might prove useful for others.

STRAIN OF BACILLI USED

The strain of rat leprosy bacilli employed was provided by Dr. E. L. Walker (Dec. 11, 1934). During the six years of passage of this strain through rats in this laboratory, the percentage of animals showing nodules has decreased, and the interval between inoculation and the appearance of nodules has increased. Yet Emerson, Anderson and Leake,[3] employing a strain freshly obtained from wild rats with spontaneous leprosy, made ten passages at intervals of six months without observing any alteration in virulency.

PROMIN

Promin[4] is the sodium salt of p,p′-diaminodiphenylsulfone-N,N′-di-(dextrose sulfonate) and has the following structure:



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From the Anatomical Laboratory, Washington University, and the Barnard Free Skin and Cancer Hospital.

(Footnotes continued on next page)

Dr. Walter M. Simpson suggested that its influence should be tested on the development of rat leprosy nodules. After our work with promin had been started, a paper appeared by Feldman, Hinshaw and Moses [5] reporting that in experiments on tuberculosis of guinea pigs the animals treated with promin survived longer and showed less extensive lesions than untreated controls. Promin has, moreover, been used to advantage in pneumococcic [6] and gonococcic [7] infections.

PROCEDURE FOR PROMIN

Fifteen pairs of rats were selected March 27, 1940 from a group which had been inoculated with bacilli June 20, 1939. Every animal had a single discrete leprous nodule at or near the site of inoculation. The two constituting each pair were chosen because of similarity in their weight and in the size of their nodules. One member of each pair was treated with promin, while its mate was held as an untreated control. The diet and living conditions of the 15 treated and the 15 untreated rats were as nearly as possible identical throughout the experiment.

The treatment consisted of daily subcutaneous injections of promin (40 per cent solution, p_H 5.6-6.0) alternately in the back and abdominal regions, not into or in the immediate vicinity of the nodules. The amounts injected were: 0.2 cc. (twenty-seven days), 0.3 cc. (two days), 0.4 cc. (five days), 0.5 cc. (four days), 0.6 cc. (four days), 0.7 cc. (four days), 0.8 cc. (three days) and 0.5 cc. (eighty-eight days). During these one hundred and thirty-seven days, some of the treated animals and some of the controls died. Whether we were to continue the treatment, or whether we were to stop treatment and simply observe the results, valuable data would be secured; but the animals would probably continue to die off. To restrict our histologic comparison of treated and control animals to those which died in the course of the experiment would, however, be a serious handicap. We decided, therefore, to kill all survivors after one hundred and thirty-seven days so that the histologic examination could include well preserved tissues, unobscured by death changes, from a sufficient number of animals to prove worth while.

To measure alterations in the size of the nodules, we employed the same method that is often used for transplantable tumors. That is, the maximum length and the maximum width at right angles to the length were measured in millimeters by means of calipers, and a figure representative of size was obtained by adding the two together. Unfortunately, the nodules were more irregular in shape and exhibited less distinct margins than most transplanted tumors. It was found that

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1. Walker, E. L., and Sweeney, M. A.: J. Prev. Med. **3**:325, 1929.

2. Cowdry, E. V.: Am. J. Path. **16**:103, 1940.

3. Emerson, G.; Anderson, H. H., and Leake, C. D.: Proc. Soc. Exper. Biol. & Med. **30**:150, 1932.

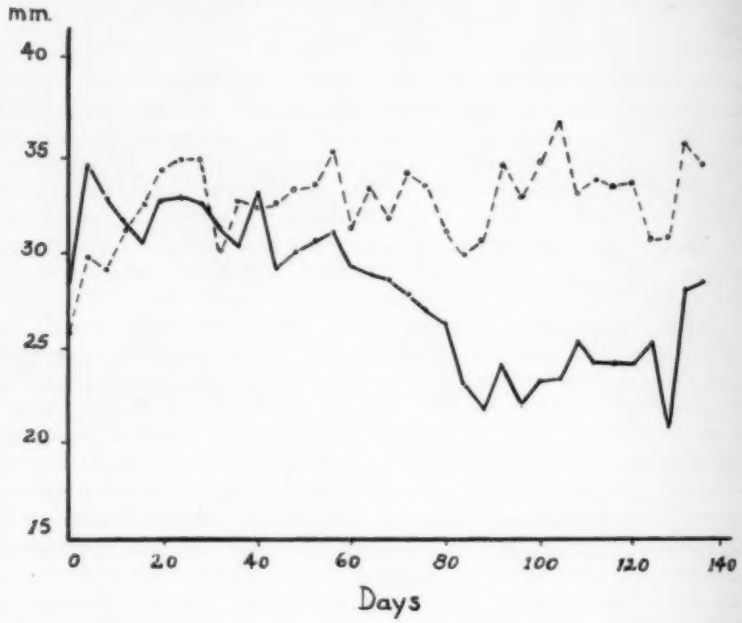
4. This preparation was supplied by Dr. E. A. Sharp of Parke, Davis & Company, Detroit.

5. Feldman, W. H.; Hinshaw, H. C., and Moses, H. E.: Proc. Staff Meet., Mayo Clin. **15**:695, 1940.

6. Greey, P. H.; MacLaren, D. B., and Lucas, C. C.: Canad. M. A. J. **40**: 319, 1939.

7. Kendell, H. W.; Rose, D. L., and Simpson, W. M.: J. A. M. A. **116**:357, 1941.

stretching of the skin while the animal was being held during measurement temporarily increased the length of the nodule. When the skin was relaxed, it, and sometimes the nodule, folded slightly and the measurements tended to be too small. Consequently, tension on the skin was made as uniform as possible. The animals were at times held by two different persons, but, for the sake of uniformity, all the measurements were made by the junior author. The depth of the nodules was not taken into consideration, but it was fairly uniform in the case of the smaller ones, which were freely movable over underlying muscle. When a nodule underwent central necrosis with liquefaction and discharged on the surface, the dimensions as measured tended to decrease, because the margins were no longer held apart. Indeed, if fibrosis progressed, they were drawn closer together. But the amount of



Size of nodules in promin-treated animals (solid line) and in controls (broken line) after various intervals of time.

living tissue laden with bacilli was not necessarily decreased. When a nodule discharged into the abdominal cavity—a much rarer occurrence—its size was modified in the same way, but death usually followed in a week or two. Our first measurements were less accurate than the later ones, because at the beginning we did not fully appreciate the sources of experimental error in making them.

GENERAL OBSERVATIONS ON EFFECT OF PROMIN

The figures for size of nodule, determined every fourth day for each rat, were averaged for the treated and the control rats and were plotted in millimeters against time in days in the chart. Some animals did not

survive the one hundred and thirty-seven days (table 1), so that the number of nodules measured decreases. The average size of nodules in the treated animals is indicated by a solid line and that of the nodules in the controls by a broken line. In general the solid line is below the broken line despite the fact that the initial size of the nodules in the treated animals was found to be a little larger. However, the difference in size of nodules between treated and control animals during this long period was comparatively slight.

In the first column of table 1 are given the numbers assigned to each pair of rats. In the second column are given the numbers of days of survival of the treated members of each pair after treatment was started.

TABLE 1.—*Survival Time*

Rat Pair	Days Treated Rat Survived After Beginning Treatment	Days Control Mate Was Left Untreated
1	137*	79
2	60	36
3	137*	45†
4	124	100
5	1	39
6	137*	137*
7	41	137*
8	137*	20
9	137*	137*
10	137*	137*
11	133	137*
12	137*	20
13	4	2
14	124	113
15	137*	119
	1,583	1,258

* The animal was alive at the end of the experiment.
† The animal was killed during the experiment. The others died during the experiment.

In the third column are presented the numbers of days of survival of the untreated members of each pair after treatment of their mates was started. Those that survived when the experiment was concluded after one hundred and thirty-seven days and were then killed in order that we might collect material for histologic examination are indicated with an asterisk. The treated rat of the fifth pair was found to have been pregnant. The untreated rat in the third pair was put to death on the forty-fifth day (marked †) to provide organisms for the inoculation of another series of rats. The treated rat of the fourteenth pair looked healthy before its last injection but died with convulsions a few minutes later. This occurrence was the only sign observed of possible danger in the treatment.

The number of rats which survived treatment was 8, compared with 5 control rats which lived for an equal period. Taking the treated rats as a whole, the survival time was one thousand, five hundred and eighty-

three days, compared with one thousand, two hundred and fifty-eight days—a difference of three hundred and twenty-five days. If the control animal killed for material had not been removed from the series but had managed to live ninety-two days longer, the difference would have been less. The surviving treated animals at one hundred and thirty-seven days appeared to be in better condition than the controls. Their average weight was 65.1 Gm. heavier.

HISTOLOGIC OBSERVATIONS ON EFFECT OF PROMIN

At autopsy of the surviving rats, certain tissues were excised and fixed in a 37 to 40 per cent solution of formaldehyde diluted 1 : 10. Their bodies, with viscera exposed, were carefully preserved in the same fluid for further study if necessary. Solution of formaldehyde was used because it is a good general fixative and penetrates quickly and well. It was important to have uniformity of action not only on the cells near the surface but also on those situated more deeply, as well as in all of the specimens of the series. The freezing and drying method is superior for shape of bacilli,[8] but to have employed it throughout would have been cumbersome. All sections were cut 5 microns thick and were stained with carbolfuchsin and Harris' hematoxylin.

Nodules.—No consistent differences were observed in the structure of the nodules in treated and control rats. A single large area of central necrosis, or several small ones, was found in every nodule except in that of the treated member of the sixth pair. Leukocytic infiltration accompanied the necrosis about equally in both sets of specimens. Peripheral lymphocytic infiltration, present in some nodules and absent in others, was not noticeably different.

Since intracellular accumulations of bacilli, called rosettes, may be a phase in the life cycle of the organism, a search was made for them. None as well formed as those previously reported [9] in this strain of rat leprosy were found in any of the nodules, but the rosettes were more conspicuous in two untreated nodules than in any of the treated ones. Otherwise no difference was observed in the rosettes.

Though the significance of the homogeneously staining long smooth bacilli and the granular forms is not clear,[10] it seemed desirable to discover whether there was a difference in the occurrence of these types in treated as compared with control nodules. Both sets of nodules exhibited such marked local variations in the bacilli that it was necessary to compare as nearly as possible similar areas in all of the nodules:

1. The bacilli at the peripheries of the nodules, in areas provided with blood vessels and uncomplicated by lymphocytic or leukocytic infil-

8. Cowdry, E. V., and Heimburger, L. F.: Proc. Soc. Exper. Biol. & Med. **32**:1422, 1935.

9. Cowdry, E. V., and Ravold, A.: Puerto Rico J. Pub. Health & Trop. Med. **14**:3, 1938.

10. Cowdry, E. V.: Puerto Rico J. Pub. Health & Trop. Med. **14**:95, 1938.

tration, were usually longer and less granular than those in the deeper parts in both treated and control nodules. The degree of granularity in the peripheral location appeared to be in general slightly greater in the treated animals. In 1 treated animal (no. 6) it was much greater.

2. The bacilli in areas intermediate between the periphery and the necrotic foci did not differ noticeably in degree of granularity in treated and control animals.

3. The bacilli within the necrotic foci were approximately the same as to shape and size in both series. In some nodules the polymorphonuclear leukocytes were more heavily laden with bacilli than in others, but this difference was manifest in control as well as in treated animals.

Other Tissues.—The following tissues from all of the 8 surviving treated rats and 5 controls were examined: spleen, lung, kidney, adrenal, ovary (or testicle), stomach, small intestine, pancreas, large intestine, skeletal muscle and heart. In addition, the livers from all animals except 1 treated animal were examined.

Spread of bacilli from the nodules to other parts of the body was but slight. They were observed only in the spleen, liver and lungs, but further search might have revealed some in still other locations. Their occurrence in these organs was about the same in treated and control rats: They were seen in the spleen in 2 treated rats and 2 controls, in the liver in 1 treated rat and no controls, and in the lungs in 1 treated rat and 2 controls. When present outside nodules, bacilli were in approximately the same number in treated rats and controls. Otherwise the tissues of both series of rats were remarkably free from lesions. Only slight leukocytic infiltration was observed in the lungs of 1 control, and moderate fatty degeneration of the liver, in 4 treated rats and 2 controls. These differences we do not consider significant in such small experimental series. No sign was noted of the action of an "inapparent" virus sometimes present in the kidneys of rats. It is not to be expected that histologic examination would yield data on the better condition of the treated rat indicated by their heavier weight.

STARCH

Injections of starch were made for several reasons. Chambers and Grand [11] found that they cause infiltration by polymorphonuclear leukocytes and healing of a considerable percentage of rat sarcoma 180. Leprous nodules are not neoplasms, but they are due to an accumulation of cells, which, like the sarcomatous cells, are of mesenchymatous origin. Both the leprous nodule and sarcoma are chronic, very cellular lesions, not rich in blood vessels. Since there is often marked leukocytic infiltra-

11. Chambers, R., and Grand, C. G.: Am. J. Cancer **29**:211, 1937.

tion in the lesions of tuberculoid leprosy in children, from which many recover, and conspicuously little in the lesions of lepromatous leprosy of older people, which is usually fatal, it seemed quite possible that promotion of infiltration of leukocytes by injections of starch might be helpful. It was thought also that if the neutrophils provide food substances (trephones) for fibroblasts, as Carrel [12] has reported, their presence in increased numbers might serve a good purpose in accelerating fibrosis. After we had started to experiment with starch, the suggestion was made to Dr. R. L. Kile that it would be worth while to inject starch into the cutaneous nodules of lupus vulgaris—a chronic condition in which the nodules contain cells of the same kinds as those in leprosy—caused, like leprosy, by acid-fast bacilli but of a different sort. The remarkable healing of lesions which he secured [13] was encouraging, but much work on our part was unsuccessful and only a brief summary will be presented.

Thirty rats were selected, each bearing a subcutaneous nodule of about the same size. Sixteen of these received injections of 1 per cent corn starch in physiologic solution of sodium chloride (prepared as specified by Chambers and Grand) directly into the nodules, while 14 were set aside as untreated controls. The dose of starch was from 0.1 to 0.2 cc.; the interval was usually four to seven days, and from two to twenty-five injections were made into a single nodule. When, as often happened, the centers of the nodules liquefied, owing to accumulation of leukocytes and necrosis, the contents were aspirated by means of a syringe with a needle of large bore. Occasional nodules in both treated and control animals ulcerated. These were painted with 1 per cent methylthionine chloride (methylene blue) to keep down secondary infections.

In several instances fibrosis occurred in large ulcerating nodules, 4 to 5 cm. in diameter flattened out, the epidermis grew over from the sides, hair developed in the new formed epidermis and the healing appeared for several weeks to be complete. One such animal was under observation for three hundred and thirty-four days after treatment. But healing of this type took place with equal frequency in the controls, and in both groups it was always temporary. At the sides of the apparently healed nodules tiny secondary nodules grew and enlarged. Some of these in the experimental series were treated with starch but without success. There is no evidence that the injections of starch were either beneficial or injurious. However, if the injection is not done quickly, the starch grains have a tendency to settle and even to clump in the needle. In the treatment of lupus, veins must be carefully avoided on the chance that the starch introduced might produce emboli.

12. Carrel, A.: J. A. M. A. **82**:255, 1924.
13. Kile, R. L.: Arch. Dermat. & Syph. **39**:471, 1939.

HEPTALDEHYDE

The feeding of heptaldehyde (heptyl aldehyde) was found by Strong [14] to produce liquefaction of spontaneous tumors of the mammary glands in mice "so intense that in some cases drainage through a hypodermic needle was easily accomplished." This was accompanied by frequent regression of the tumors—a result not unlike that obtained by Chambers and Grand with starch and one which indicated that the influence of heptaldehyde on rat leprosy nodules should be tested. Moreover, Carruthers,[15] working in our laboratory, has induced resorption of mouse

TABLE 2.—*Promin Treatment in Leprosy and Tuberculosis*

	Rat Leprosy (Our Series)	Guinea Pig Tuberculosis (Feldman, Hinshaw and Moses' Series)
Method of treatment	Drug given by subcutaneous injection	Drug given with food; absorption proved by chemical analysis of blood
Start of treatment	280 days after inoculation with leprosy bacilli, when nodules had developed; disease was therefore well established	Guinea pigs first received promin, which was found in appreciable concentration in their blood. Then promin was omitted from their diet for "several days." Two days after resumption of promin feeding the animals were inoculated with a suspension of tubercle bacilli
Duration of experiment	137 days	164 days
Rats surviving at end of experiment	8 of 15 treated rats 5 of 15 controls	13 of 20 treated rats 0 of 20 controls
Condition of surviving animals	That of treated rats better than that of controls as shown by average weight; treated ones 65.1 Gm. heavier	Weights not given
Gross size of lesions	Average size of nodules slightly less in treated rats than in controls	Not measurable
Organ involvement	Including only survivors: Few bacilli in spleen of 2 treated rats and 2 controls, in liver of 1 treated rat and no controls, and in lungs of 1 treated rat and 2 controls	Including survivors plus those dying during experiment; only spleen examined: 18 of 29 treated rats showed lesions. All of 20 controls showed lesions

embryos by adding heptaldehyde to the diet and has pointed out to me that the formula of heptaldehyde suggests that it may act on the waxy components of the acid-fast bacilli of rat leprosy. However, the results, like those with starch, were negative and will therefore be reported even more briefly.

Fifty-three rats were chosen: 4, at two hundred and twenty-four days after inoculation; 12, at one hundred and five days; 22, at nineteen days, and 15, at seven days. In the last two groups there were as yet no leprous nodules. These groups were included to test the influence of heptaldehyde on recently inoculated bacilli before they had time to establish themselves. Only 19 of the rats were left untreated as controls. Heptaldehyde, less than one month after its

14. Strong, L. C.: Am. J. Cancer **35**:401, 1939.

15. Carruthers, C.: Proc. Soc. Exper. Biol. & Med. **41**:336, 1939.

receipt from the Eastman Kodak Company, was injected into the nodules as in the experiment with starch except that the dose was smaller (0.1 to 0.05 cc.) and the injections were fewer (not more than four in each nodule). Methylthionine chloride (methylene blue) was again used for the nodules that ulcerated.

No beneficial results were observed. The nodules already developed continued to increase in size, and some underwent central necrosis and liquefaction, while at the sites of injection in recently inoculated animals nodules formed as in the controls. In the recently inoculated animals, particularly, small areas of epidermis, including the needle punctures, dried and sloughed off. The fact that a rat died a few seconds after receiving an injection and another two minutes after, and that the mortality in the treated rats was greater than in the controls, shows that the procedure was definitely dangerous, as was indeed to be anticipated.

COMMENT

Table 2 gives a comparison of our results with promin in experimental leprosy with those obtained by Feldman, Hinshaw and Moses in experimental tuberculosis. Ours were evidently not so favorable as theirs. Both show that promin is a drug which can be administered over a long period without any debilitating effect, which is an important consideration in studies on the chemotherapy of both leprosy and tuberculosis.

SUMMARY

Repeated subcutaneous injections of promin in a small series of leprous rats modified the course of development of the nodules little if at all; but the survival time of the treated animals was somewhat longer than that of the controls, and at the conclusion of the experiment the treated animals were definitely in better condition than the controls. Some nodules healed temporarily after intranodular injections of starch, but so also did some untreated nodules. No evidence was found that intranodular injections of heptaldehyde, or injections of heptaldehyde into areas previously inoculated with bacilli before sufficient time had elapsed for nodule development, were beneficial.

TUBERCULOUS SPONDYLITIS

A HISTOLOGIC STUDY

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DENVER

Present knowledge of the structure of vertebral tuberculosis is mainly derived either from roentgenologic and gross pathologic studies or by inference from the changes which are known to take place in more accessible bones and joints. On account of the difficulties involved in preparing large sections for histologic investigation, pertinent communications concerning the histologic phase of the problem are few. It is the purpose of this paper to present the microscopic observations in 13 cases of tuberculous spondylitis.

The patients consisted of 3 children, aged respectively 4, 5 and 14 years, and 10 adults, the oldest of whom was 84. Of these, 6 were males and 7 females. The duration of the disease ranged from one and one-half to thirty-two years. The lumbar vertebrae were affected in 6 patients, the thoracic in 4 and the cervical in 2 patients. One specimen of tuberculosis of the sacrum and coccyx was included. The material was prepared by the method of Bock.[1]

MICROSCOPIC OBSERVATIONS

A detailed study of each section was made. The changes which were noted in the 13 cases differed from one another only in degree or extent. The data, therefore, will be presented as a whole, and the various parts will be illustrated by particular lesions in the individual cases. For convenience the changes will be grouped under headings which represent the various components of the vertebral body.

Longitudinal Ligaments.—No differences were noted in the lesions of either the anterior or the posterior longitudinal ligament. Where bone destruction was extensive, the ligaments were the seat of marked lymphoid infiltration and epithelioid cell reaction throughout. These areas often contained foci of caseation. The character of the ligamentous structure was usually completely masked. Exudate of similar character was noted in adjacent adipose tissue. The inflammatory zone of the ligament was sometimes in direct contact with the cortex and sometimes was separated from it by a dense fibrous band which apparently represented compression of the periosteum. The interposed fibrous layer, when present, was usually free of inflammatory exudate. The degree of cellular invasion of the ligament

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1. Bock, N.: Ztschr. f. wissensch. Mikr. **40**:318, 1923.

became gradually less as one proceeded in either direction from the seat of greatest involvement, disappearing last in the deeper layers, where it persisted finally as a collar about the engorged vessels. It was noteworthy how abruptly the tuberculous process stopped in a few of the specimens.

Intervertebral Disk.—Resorption of the intervertebral disk occurred early in the course of the disease. In several instances the disk had almost entirely dis-

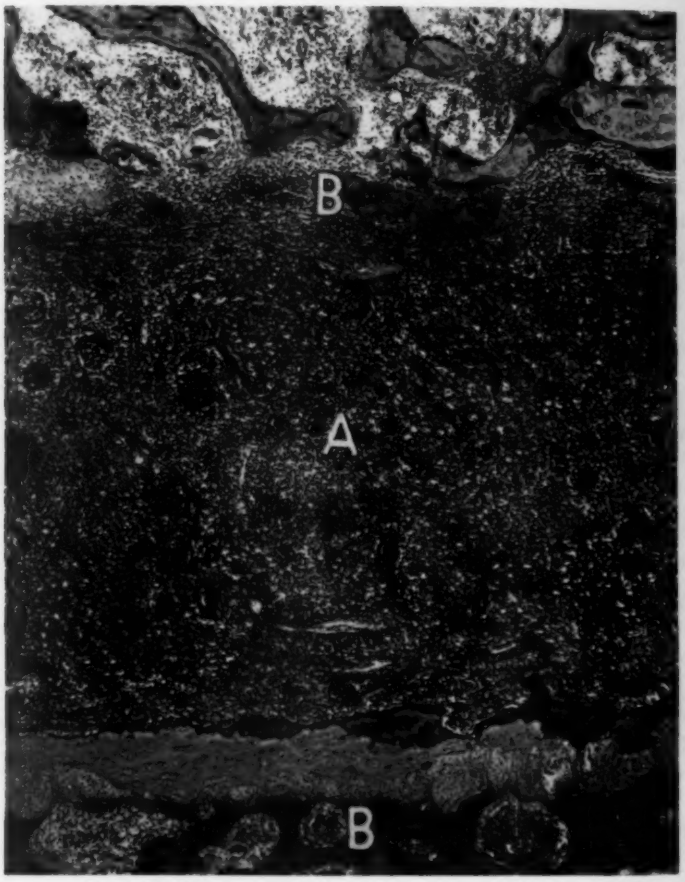

Fig. 1.—Almost complete destruction of an intervertebral disk (*A*), with contiguous bone plates (*B*) essentially intact; × 48.

appeared before the endochondral bone plates had been damaged to any great extent (fig. 1). The disk appeared to be invaded in either one or both of two ways: (1) by extension of the tuberculous process from the longitudinal ligaments; (2) by extension from the subchondral marrow spaces. In the former, resorption seemed to have begun in the fibrocartilaginous portion with an irregular excavation of the margin of the disk and to have extended rapidly along the central region (fig. 3). In the latter, the articular cartilage appeared to have

been invaded from the subchondral marrow spaces after destruction of an area of the bone plate. Resorption of the contiguous hyaline cartilage seemed to have taken place at a much slower rate than when the fibrocartilage was primarily involved. Fibrocartilage is apparently resorbed with greater ease than hyaline cartilage. Numerous examples were noted in which the former type of cartilage had disappeared over a larger area than the hyaline portion of the disk.

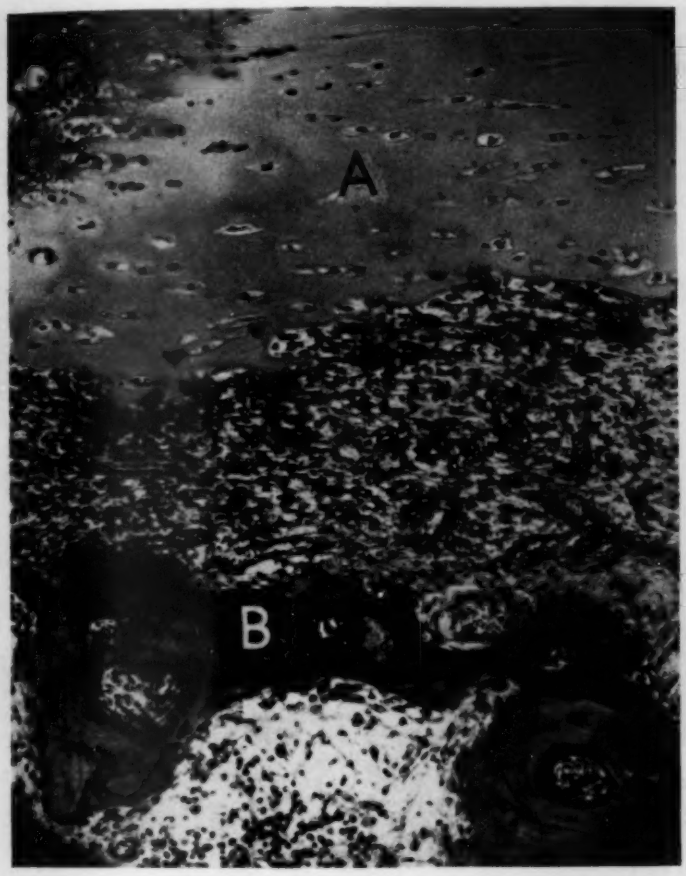

Fig. 2.—Beginning destruction of a hyaline portion of a disk (*A*), with intact bone plate (*B*); × 170.

The fibrocartilage was destroyed by incomplete resorption. The edges of the cartilage assumed a fimbriated or eyelash appearance; no single or multinucleated chondroclasts were found. Dissolution of the hyaline cartilage, however, was brought about either by incomplete or by complete resorption. The former type predominated in all sections. The intervertebral disk which had been resorbed was replaced by tuberculous granulation tissue, in which hyaline remnants were occa-

sionally observed. In some fragments the cells exhibited karyolysis and cytoplasmic granularity. The margins of the lacunas remained sharply defined. In others pyknosis was noted. Where karyolysis was present, it was difficult in many instances to distinguish the nucleus from the coarsely granular cytoplasm, which did not completely fill the lacuna. The lacunar edges, instead of being smooth and sharply defined, were indistinct and granular. Such marked changes signify death of the cell, and the remnants in which they were found might be termed cartilaginous sequestrums (fig. 4).

Areas of regenerating cartilaginous tissue were found, the earliest recognizable stages of which comprised a collection of cells with large round to oval vesicular nuclei, one or more nucleoli and narrow rims of pink-stained cytoplasm. It was

Fig. 3.—Early invasion of a fibrous portion of a disk from the adjacent longitudinal ligament; × 6.4.

difficult to distinguish these young cartilage cells from fibroblasts in the immediate neighborhood. The matrix was definitely fibrillar. On tracing the regenerative stage further, the matrix became more compact and its fibrillar structure less marked. The ground substance then became homogeneous and stained deeply with eosin; the contained cells were fewer. Occasionally, irregular deposits of calcium granules were found peripherally in some of the cells. In all instances the foci of regeneration were attached either to small remnants of adult hyaline cartilage still adherent to trabeculae of the endochondral bone plate or to hyaline fragments of disk cartilage.

Cysts and cartilage islands found along the margin of the disk are changes of lesser importance and are not specific to tuberculosis. The number of cysts did not appear to be related directly to the damage suffered by that disk.

Cortex.—The most extensive subperiosteal changes were noted especially in the regions where the densely cellular and caseous zones of the ligament were in direct contact with the cortex. The cortical margins were deeply grooved with Howship's lacunas, many of which contained large, multinucleated osteoclasts. In these areas the layer of osteoblasts was absent. The superficial osteocytes had undergone certain degenerative changes, evidenced by their faint staining quality and pyknotic

Fig. 4.—Destruction of a hyaline portion of an intervertebral disk (*A*), with a resultant cartilaginous sequestrum (*B*); × 170.

nuclei. Many lacunas were empty. In some areas the cortex had been converted into small sequestrums. Wherever the ligamentous inflammatory zone was separated from the cortex by a compact band of fibrous tissue, cortical damage was less marked, and osteoblasts formed a continuous cover. The margins even here were somewhat serrated by osteoclastic activity; the serration was not so marked, however, as under the former conditions. Occasionally, the bone edges were smooth. The superficial osteocytes showed no signs of degeneration.

Several examples of direct invasion of a body by the granulomatous process from the ligament were noted, this occurring for the most part at the epiphysial angle where the cortex is thinnest. Entrance into the contiguous marrow spaces had usually been preceded by widespread damage of the cortical trabeculae.

New bone formation along the cortical margin was not unusual. It must be emphasized, however, that this was not a prominent feature. The newly formed bone was seen either as narrow uncalcified zones (osteoid tissue) laid down parallel to the lamellas of the cortex or as small newly formed trabeculae which projected from the cortical surface. The former type predominated. The periosteal outgrowths were usually surrounded by hypertrophic osteoblasts. No young bone was noted in any area where the caseous zone of the ligament was in direct contact with the cortex. The inflammatory cell infiltration alone had apparently not inhibited regeneration. The "bony ridges" of Cofield [2] were sought in every section; none were found.

Trabeculae of the Substantia Spongiosa.—The destructive changes in the trabeculae were intimately associated with the presence of tuberculous granulation tissue. Where caseation occurred in the region of trabeculae without directly involving their margins, osteoclastic resorption was widespread. Where caseous areas lay in direct contact with the trabeculae, the margins of the bone were usually smooth, no osteoblasts could be identified and there were degenerative changes in the osteocytes. Osteocytic death was limited to the areas where the osteoblasts had disappeared. Here one gained the impression of a rapidly progressing lesion, and it seemed that a toxic agent, probably liberated by the tubercle bacilli, had destroyed the osteoblasts, osteoclasts and osteocytes. This picture is similar to that found in cases of active pyogenic osteomyelitis.

A local increase in the number of trabeculae was found in one specimen. It was observed at the posterosuperior segment of a body, the intervertebral disk of which had been extensively resorbed. There were no structural abnormalities in the individual trabeculae. The marrow spaces were the seat of fibroblastic proliferation. It might appear that there was primarily a compensatory reenforcement of the body in the face of the disk destruction, although had this been true one should have found the same change in all sections presenting marked resorption of the disk.

In 1 case the trabeculae in the second and third sacral segments were very bulky. They contained numerous cement lines. A close reticulum had been formed, with consequent encroachment on the marrow spaces. The osteoblasts here were not hypertrophied, however, and narrow uncalcified zones of new bone were few. There were numerous osteoclasts along the anterior and posterior margins of the body, where the sclerosis had advanced to the point of eburnation. The activity of the tuberculous process in these segments appeared to be of a low grade.

An occasional narrow zone of new bone bordered those trabeculae of the endochondral bone plates which had been denuded of disk cartilage. The formation of new bone took place in the presence of specific inflammatory cell elements only in the event that the inflammatory or caseous process was not in direct contact with the trabeculae.

Only one example of actual new growth of trabeculae was encountered. They contained numerous osteocytes arranged in an irregular manner and presented a border of closely spaced large round osteoblasts. This osseous proliferation bordered an extensive active tuberculous focus, the periphery of which consisted of a

2. Cofield, R. B.: J. A. M. A. **79**:1391, 1922.

loose network of fibroblasts. The newly formed trabeculae did not appear to have been a response to healing of the lesion but may have represented a second line of defense.

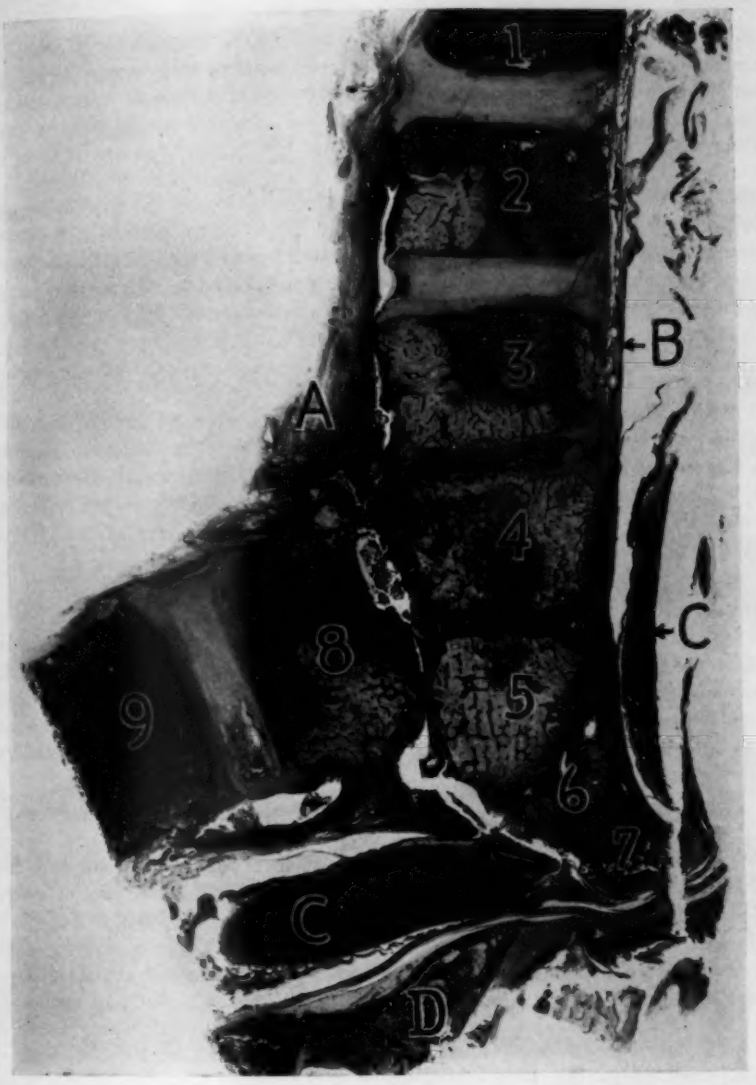

Fig. 5.—Section of tuberculous spondylitis of the thoracic region (× 1.6), showing marked kyphosis. The patient was a girl aged 5. Note the destruction of disks between vertebrae 4 to 8 inclusive, with almost complete disappearance of the disks between vertebrae 3 and 4. The light areas in bodies 2, 3, 4, 5 and 8 consist of fibrous tissue. Other anatomic features are: *A*, anterior longitudinal ligament; *B*, posterior longitudinal ligament; *C*, spinal cord; *D*, lamina.

Atrophic changes in the substantia spongiosa were found in several cases, the trabeculae being slender and the osteoblasts small and spindled. The margins were smooth and the marrow spaces widened. Trabecular atrophy occurred mainly in areas where the tuberculous process was no longer active or in essentially uninvolved regions at some distance from the site of infection.

Bone Marrow.—The early neutrophilic leukoblastic reaction, or the so-called acute reactionary stage, which lasts about one hundred and twenty hours,[3] was not observed in this group, on account of the duration of the disease in each instance. The cytologic character of the tuberculous lesion per se in the marrow cavity differed nowise from that in any other tissue. In progressive lesions there was no sharp boundary between the inflammatory and the hemopoietic elements, the lymphocytes and epithelioid cells merging imperceptibly with the myeloid elements. Cells of the granulocyte series were usually in excess of normal in uninvolved areas. Noncaseous tuberculous foci were not surrounded by a fibrous zone, fibroblasts first appearing in areas where caseation necrosis had taken place and forming in the early stages a loose avascular network, which contained but few inflammatory cell elements. With condensation of the network, fibrocytes were more numerous than fibroblasts, and many newly formed capillaries appeared, the whole generously infiltrated by a granulomatous cell exudate.

Where the longitudinal ligament was markedly involved in the tuberculous process, the contiguous subcortical marrow spaces exhibited complete replacement of hemopoietic elements by specific inflammatory cells, even though the remainder of the vertebral body appeared normal. In the same degree as the tuberculous process of the ligament ceased, the marrow contents appeared normal. Healing areas were marked by eosinophils and plasmocytes.

Blood Vessels.—Obliteration of the lumens of capillaries and arterioles in caseous regions was the most frequent finding as regards blood vessels. In the larger vessels proliferation of the intima, media and adventitia was present, although not to the extent seen in syphilis. A prominent lymphocyte–epithelioid cell collar was often noted. In the marrow spaces which had undergone fibrosis, capillaries were most numerous; these vessels appeared normal. Areas of hemorrhage were few, located mainly about areas of caseation necrosis. Deposits of hemosiderin granules were also present.

Vertebral Appendages.—The spinous processes and their ligaments were present in 3 cases in which kyphosis of varying degrees was noted; in 2 of these instances the spinous processes exhibited no pathologic change despite the damage to their respective bodies. In the third case, however, the spinous processes were extensively involved in the region of a right angle kyphotic deformity, which was due to complete anterior dislocation of two vertebral bodies. They contained caseating tuberculous granulation tissue. The ligaments were intact and contained only a scant number of inflammatory cells. In a fourth case a portion of lamina was attached to the upper edge of a body which was normal in shape, the tuberculous lesion in this instance being situated in the upper third of the body. Osteoclastic activity was marked along the cortical margins of the lamina, and the marrow spaces had undergone fibroblastic proliferation with sparse interspersion of chronic inflammatory cells. The ligament was slightly involved as well.

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3. (*a*) Fraser, J.: Tuberculosis of the Bones and Joints in Children, London, Adams & Charles Black, 1914. (*b*) Loeffler, F.: Ergebn. d. Chir. u. Orthop. **15**: 391, 1922.

Miscellaneous Findings.—Varying degrees of calcification of caseous foci were encountered; often this process was very extensive.

Several sections showed pockets of serous exudate, located in dense tuberculous areas, some of which had undergone caseation. No definite lining cells were found, the collections being bounded usually by fibroblasts; in some instances the young connective tissue cells extended into the exudate.

COMMENT

The 13 cases reported in this study did not warrant any classification of the various types of tuberculous spondylitis.[3] In the majority of the cases the disease was of long duration and the pathologic changes were widespread throughout the vertebral body. It could not be ascertained whether the primary site of the infection in any case was in the intervertebral disk or in an appendage, although both types of origin apparently are observed.[4]

Compere and Garrison [5] studied 4 cases of uncomplicated tuberculosis of the spine, reporting that "cartilage is less readily destroyed than is bone." Our observations did not corroborate this statement. Among the most striking features were the apparent ease and rapidity with which the intervertebral disk was destroyed, the fibrocartilage and the nucleus pulposus being the first structures to disappear. The remnants of the disk cartilage which were found consisted of hyaline cartilage alone. Such tissue remnants might be called cartilaginous sequestrums. The fibrocartilage was destroyed by incomplete resorption; the hyaline cartilage either by complete or by incomplete resorption. No instance was found in which an intervertebral disk was completely intact when the contiguous bodies were involved to any extent by the tuberculous process.

In extension of the disease from one vertebral body to another along the longitudinal ligaments, invasion of the articular disk usually appeared to have preceded involvement of the body. It is also noteworthy that despite marked damage to the disk the trabeculae of the endochondral bone plate may remain essentially uninvolved. This feature has been stressed from a roentgenologic standpoint by George and Leonard.[6]

Various degrees of herniation of the nucleus pulposus into the respective contiguous bodies were noted in the early stages of the progress of the disease. This occurred following partial or complete destruction of the supporting endochondral bone plate. If the process was of long standing, the nuclear material was destroyed, leaving no trace of its presence.

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4. Doub, H. P., and Badgley, C. E.: Am. J. Roentgenol. **27**:827, 1932. Beneke: München. med. Wchnschr. **55**:1105, 1908.

5. Compere, E. L., and Garrison, M.: Ann. Surg. **104**:1038, 1936.

6. George, A. W., and Leonard, R. D.: Ann. Roentgenol. **8**:39, 1929.

Although tuberculosis of bone is primarily a destructive disease, small areas of new bone formation were not an unusual finding. In a case of sacral involvement a local increase in the number of trabeculae of the substantia spongiosa was encountered. This feature, however, did not play a prominent role in the reparative process. Fraser [3a] stated that "the process of osteosclerosis is indicative of the more chronic types of bone disease; its objective is a limiting one, but a more passive limitation than that of fibrous marrow for example." The duration of the disease in this case was fourteen years. In 3 other cases in which the history covered a period of ten years or more, osteosclerosis was absent. In the latter instances the lesion was not located in the sacrum.

Besides new bone formation, areas of regenerating hyaline cartilage were likewise encountered, and in every instance these were outgrowths from hyaline remnants of the intervertebral disk. Regeneration of cartilage apparently does not occur to any considerable extent.

Mandelstamm [7] has reemphasized that the spread of tuberculosis from one vertebral body to another may take place along the longitudinal ligaments. In a gross pathologic study he found this mode of extension to be the most frequent in his series of cases. He observed that the process might be of an ascending or a descending type. Our observations substantiate this view.

SUMMARY

Histologic data from a study of 13 cases of tuberculous spondylitis are presented.

The intervertebral disk is attacked early in the course of the disease. The fibrocartilage and nucleus pulposus are destroyed before the hyaline portion of the disk.

The intervertebral disk may be invaded either directly from the contiguous subchondral marrow spaces or from the longitudinal ligaments after these have been invaded by the tuberculous process.

Areas of regenerating osseous and hyaline cartilaginous tissues are found in the reparative stages.

Obliterative endarteritis is a frequent finding in active foci.

The tuberculous process may extend from one body to another along the longitudinal ligaments.

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7. Mandelstamm, M.: Arch. f. klin. Chir. **174**:685, 1933.

Case Reports

DIFFUSE MENINGIOMATOSIS

M. Hunter Brown, M.D.,* and James W. Kernohan, M.D., Rochester, Minn.

Recent years have witnessed an ever increasing interest in diffuse meningeal neoplasms, notably in the effort to delineate clearly the nature of these growths and, if possible, to establish the rare antemortem diagnosis. At present at least five different types of cells are known to have the capacity of establishing themselves in multiple sites throughout the leptomeninges; these are the cells of carcinomatous, sarcomatous, melanomatous, gliomatous and meningeal tumors. Examples of such neoplasms, however, have been relatively rare, and as a result knowledge has accumulated gradually through the medium of isolated reports of cases.

Although meningeal "sarcomatous" metastasis from a primary intracerebral tumor was reported by Ollivier [1] early in the nineteenth century, credit for the earliest notion of possible multiple foci of origin belongs to Schultze,[2] who issued a report on "multiple pial sarcoma" in 1880. Nonne [3] further developed this doctrine and called attention to the perithelial nature of the condition in his case. The tumor cells appeared to originate in the adventitia of pial vessels and secondarily infected the leptomeninges. Subsequent contributions were made by Schaede [4] and Markus,[5] and since 1920 perhaps more substantial examples of true perithelial sarcoma with secondary meningeal invasion have been noted by Cassirer and Lewy [6] and by Fried.[7] Flatau,[8] by the injection of sarcomatous emulsions into the cerebrospinal cul-de-sac of rats, lent experimental weight to these observations by demonstrating the susceptibility of the vascular pia to sarcomatous spread.

Using Hortega's fourth variant, P. Bailey and Cushing [9] demonstrated that cells which previously had been considered to be sarcomatous had glial staining characteristics, and Connor and Cushing,[10] in studying 2 examples of diffuse leptomeningeal tumors, pointed out that many examples of sarcomatosis previously reported represented in all likelihood

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From the Section on Pathologic Anatomy, Mayo Clinic.

1. Ollivier, C. P., cited by Nonne.[3]
2. Schultze, F.: Berl. klin. Wchnschr. **17**:523, 1880.
3. Nonne: Deutsche Ztschr. f. Nervenh. **21**:396, 1902.
4. Schaede, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:96, 1911.
5. Markus, O.: Arch. f. Psychiat. **51**:322, 1913.
6. Cassirer, R., and Lewy, F. H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **61**: 119, 1920.
7. Fried, B. M.: Arch. Neurol. & Psychiat. **15**:205, 1926.
8. Flatau, E.: Rev. neurol. **37**:987, 1921.
9. Bailey, P., and Cushing, H.: Arch. Neurol. & Psychiat. **14**:192, 1925.
10. Connor, C. L., and Cushing, H.: Arch. Path. **3**:374, 1927.

gliomatosis and, perhaps more specifically, medulloblastomatosis. At about this time Brannan,[11] in his description of what seems to be fibrillary astrocytoma, showed that more differentiated types of glioma could participate in this process. Firor and Ford [12] likewise reported examples of secondary metastasis from glioma, and in more recent years many varieties of glial tumor have been shown to have the capacity of being disseminated throughout the subarachnoid pathways under certain favorable local and general conditions. Interestingly enough, the primitive, highly malignant glioblastoma multiforme is one of the rarest offenders in this respect, a circumstance which seems to indicate that invasive tendencies and neoplastic anaplasia are less significant than the situation of the tumor and a receptive environment in the determination of this mode of spread. O. Bailey,[13] incidental to a report of circumscribed astrocytoma of the meninges which he felt had arisen in glial heterotopia, pointed out that these neuroglial nests (originally described by Wolbach [14]) should not be forgotten in consideration of the genesis of diffuse meningeal gliomatosis.

During the past decade the attention of pathologists has been attracted by a type of spreading leptomeningeal tumor which appears to represent a transformation of pia or arachnoid tissue (or both) into neoplasm, rather than a metastatic infiltration into the space between these membranes. In 1931 P. Bailey and Bucy,[15] describing a tumor (similar to the one to be reported herein) as a "sarcomatous meningioma," stated: "The leptomeninges practically everywhere are transformed into a diffuse tumor which extends to the depth of the sulci and accompanies the blood vessels a short distance into the cortex." Similarly, the case of Arlt [16] was of interest in that two solitary intracranial meningiomas were associated with diffuse meningiomatosis of the spinal cord and brain stem and in that both varieties of neoplasm were histologically benign. In the report of Willis [17] the condition likewise indicated transmutation rather than infiltration and again was marked by considerable infiltration along the perivascular spaces. Weinberger [18] recently has summarized the problem incidental to a report on a diffuse leptomeningeal tumor in which neither pia nor arachnoid tissue could be identified in the neoplastic zones. He attempted to distinguish between the two varieties and conceived of the process as being a transmutation of embryologic meningeal malformations; i. e., either of the two membranes or both may be arrested in development and converted into tumor in response to an unknown biologic stimulus. Weinberger's examples of pial meningiomatosis, however, are based on reports of typical perithelial sarcoma arising from vascular adventitia in single or multiple foci

11. Brannan, D.: Am. J. Path. **2**:123, 1926.
12. Firor, W. M., and Ford, F. R.: Bull. Johns Hopkins Hosp. **35**:108, 1924.
13. Bailey, O.: Arch. Path. **21**:584, 1936.
14. Wolbach, S. B.: J. M. Research **16**:495, 1907.
15. Bailey, P., and Bucy, P.: Am. J. Cancer **15**:15, 1931.
16. Arlt, H. G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:713, 1936.
17. Willis, R. A.: J. Path. & Bact. **47**:253, 1938.
18. Weinberger, L. M.: Am. J. Cancer **38**:1, 1940.

with secondary spread. Rather than to confuse the issue with overlapping cell types, it seems wise in view of the present state of knowledge to restrict the term "meningiomatosis" to the arachnoidal type of lesion alone and to assign purely mesodermal tumors to the category of sarcoma.

REPORT OF A CASE

A 23 year old man was admitted to the Mayo Clinic on June 17, 1940. Frank neurologic symptoms had been present only since October 1939, but for the two years prior to his registration he had suffered a variable degree of diffuse abdominal pain, bloating, nausea and anorexia and had slowly lost about 25 pounds (11 Kg.). During this period he had complained of mild subjective vertigo in association with this abdominal distress. In October 1939, a sharp, lancinating interscapular pain had developed, which seemed to extend upward into the posterior cervical region. By February 1940, definite motor symptoms had supervened, with the onset of weakness in the entire left lower extremity, associated with paresthesia and diffuse aching pain in that limb. A month later, paralysis had extended to the right leg, and the patient had become temporarily bedridden. This motor deficit proved to be fluctuating, however, and for three weeks in May 1940 he had been able to be up and about, after which paralysis deepened so that again he had been unable to walk. Intermittent twitchings of the abdominal and thigh muscles and some blurring of vision also had been noted during the two months prior to his registration. He complained of constipation and difficulty in initiating urination, as well as incomplete evacuation of the bladder, although catheterization had not been necessary.

Examination on admission disclosed a chronically ill young man with evidence of recent loss of weight. Both lower extremities exhibited flaccid diplegia, with absence of deep tendon reflexes and early hamstring contractures. Babinski, Chaddock and Oppenheim signs could not be elicited. There was no appreciable motor deficit in the upper extremities, although reflex responses were mildly diminished and were associated with suggestive tremor and incoordination on voluntary movement. The abdominal and cremasteric reflexes were absent. Sensory examination showed a fairly well defined level at the twelfth thoracic segment, below which all modalities were markedly diminished. The right pupil was slightly larger than the left, with pupillary responses intact. The optic fundi disclosed bilateral chronic papilledema of 5 diopters. Rather coarse, sustained bilateral nystagmus was present, and speech was somewhat thick and slurred in response to test phrases. Otherwise, the cranial nerves were not abnormal. Erythrocytes numbered 4,500,000 and leukocytes between 6,000 and 8,000 per cubic millimeter; the hemoglobin content was slightly reduced, to 12.0 Gm. per hundred cubic centimeters. The Hinton test of the blood for syphilis was negative. Urinalysis showed only an occasional pus cell and hyaline cast. The sedimentation rate varied between 5 and 9 mm. per hour. Roentgenologic examination of the thoracic and lumbar portions of the spinal column, centered over the twelfth thoracic vertebra, disclosed only marginal hypertrophic changes of the bodies of the tenth, eleventh and twelfth thoracic vertebrae with mild thoracic scoliosis and some degree of resultant torsion of the lumbar portion of the spinal column. Roentgenograms of the head and thorax disclosed nothing abnormal.

The diagnosis most seriously entertained was that of tumor of the posterior fossa of the skull with metastasis to the spinal cord. Metastatic malignant growth from an unknown primary source, multiple sclerosis and Devic's disease (neuroptic myelitis) also were suggested. The patient declined rapidly, despite supportive measures of dehydration by restriction of fluids and the administration of sorbitol

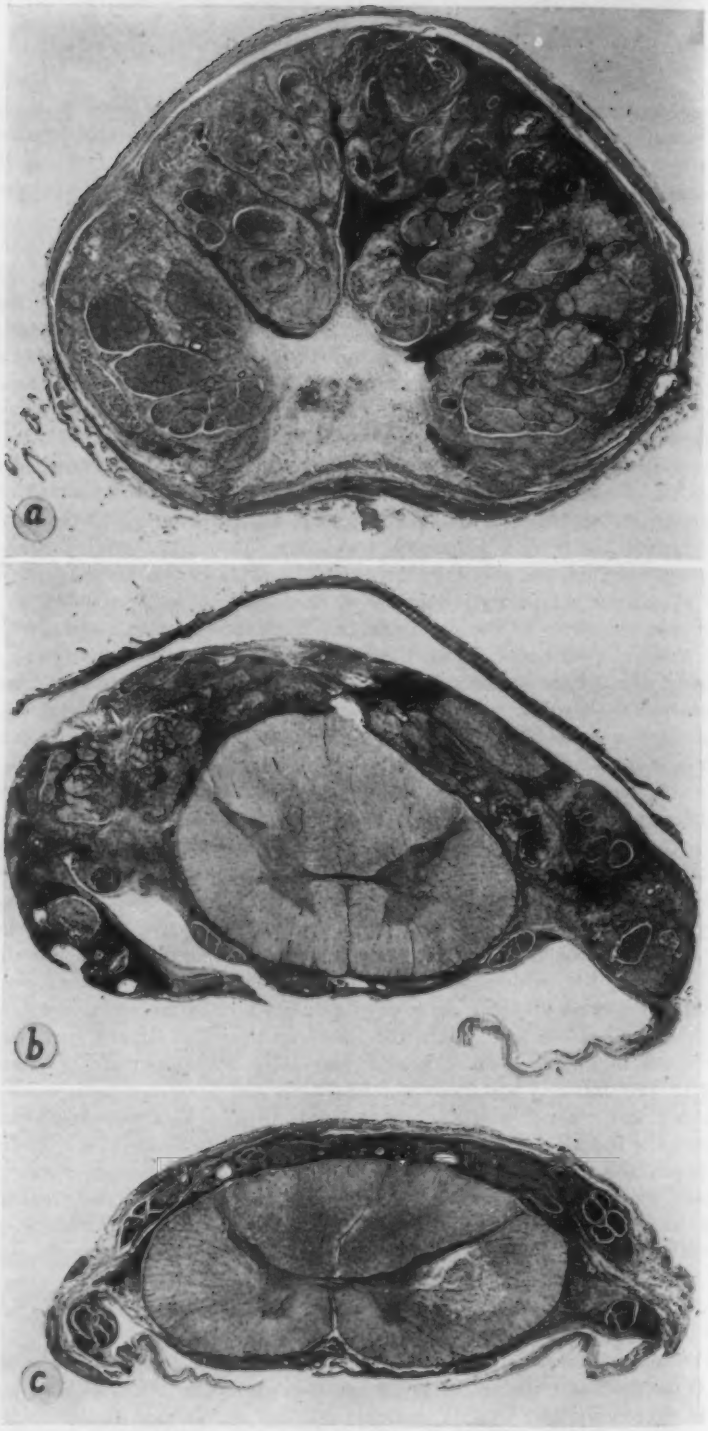

Figure 1

(See legend on opposite page)

and intensive therapy with nicotinic acid and thiamine hydrochloride. Lumbar puncture was felt to be contraindicated in the presence of a high degree of papilledema, and the patient postponed the making of ventriculograms, with possible subsequent craniotomy, pending arrival of his wife. A week after his admission he suddenly became comatose, his blood pressure collapsed and death occurred with rapid respiratory failure on June 24, 1940.

A complete necropsy was made four hours after death. No pertinent observations were made aside from those pertaining to the central nervous system. Macroscopic examination of the skull and brain showed the skull, dura, cerebral vessels and venous sinuses to be normal. The arachnoid did not appear to be unusual save for a small nodule about 5 cm. in diameter situated on the under surface of the left frontal lobe. The sulci and convolutions were not altered. The cerebellum and brain stem seemed unchanged save for a slight bloody tinge in the fluid of the cisterns and fourth ventricle. On sectioning of the brain in the frontal plane, slight uniform dilatation of the ventricular system was noted. The accessory nasal sinuses were opened and found to contain no abnormalities. When the spinal cord was removed, the overlying dura appeared to be distended with blood, but on sectioning it was found that a hemorrhagic tumor entirely surrounded the spinal cord and cauda equina from the level of the first thoracic vertebra to the conus medullaris (figs. 1 *a*, *b* and *c*). Above this segment the distribution of the tumor was more spotty. Within the cranium no gross observations were made to account for the mild internal hydrocephalus and choked optic disks.

Blocks of tissue were taken from the cauda equina, all levels of the spinal cord and brain stem and from the cerebral hemispheres and cerebellum so as to include the overlying leptomeninges. Sections of the brachial plexus were removed bilaterally, and studies on degeneration also were made on the peripheral nerves of the lower extremities, both femoral nerves and both sciatic nerves. All specimens were routinely stained with hematoxylin and eosin; in addition, the Bodian technic was employed for specimens of peripheral nerves, and the Mallory phosphotungstic acid, Mallory-Heidenhain, Weigert and Masson-Goldner [19] stains were used to study the morphologic aspects of the spinal cord and the tumor.

The neoplastic cells were round, oval or polygonal, possessed a moderate amount of finely granular cytoplasm and one or two prominent nucleoli (fig. 2 *a*). They arose from, occupied and replaced the arachnoid, and in the zones in which conversion of the tumor occurred, no arachnoid membrane could be identified as such. The cells exhibited only mildly malignant characteristics; in the numerous sections examined only a few mitotic figures were noted; there were no hyperchromatic nuclei; the cells were remarkably uniform in appearance and showed only slightly invasive tendencies. In places the nuclei assumed a vesicular, almost epithelioid appearance, growing in small clusters like grapes on a vine (fig. 2 *b*). The tumor

19. Goldner, J.: Am. J. Path. **14**:237, 1938.

Explanation of Figure 1

Sections at three different levels of the spinal cord: (*a*) The hemorrhagic tumor completely surrounds the roots of the cauda equina. (*b*) In the lower thoracic region of the spinal cord the meningeal neoplasm cuffs the cord and compresses the roots. (*c*) A more delicate sheath of tumor surrounds the spinal cord in the upper thoracic region. Note the infarction of the left lateral columns (Mallory-Heidenhain; × 6).

had no true giant cells. In general, the neoplasm was vascular and possessed an abundant reticular stroma with collagen limited to the regions about the blood vessels. Mallory's phosphotungstic acid stains disclosed no cell processes or fibrils, and there was no resemblance to a glial tumor in cellular appearances, staining characteristics or tumor pattern. In the lumbar and lower thoracic regions the neoplasm had completely encircled and severely damaged the substance of the spinal cord by compression; in the region marked off by the tenth to the first thoracic vertebrae a more delicate sheath of cells still encased the spinal cord but

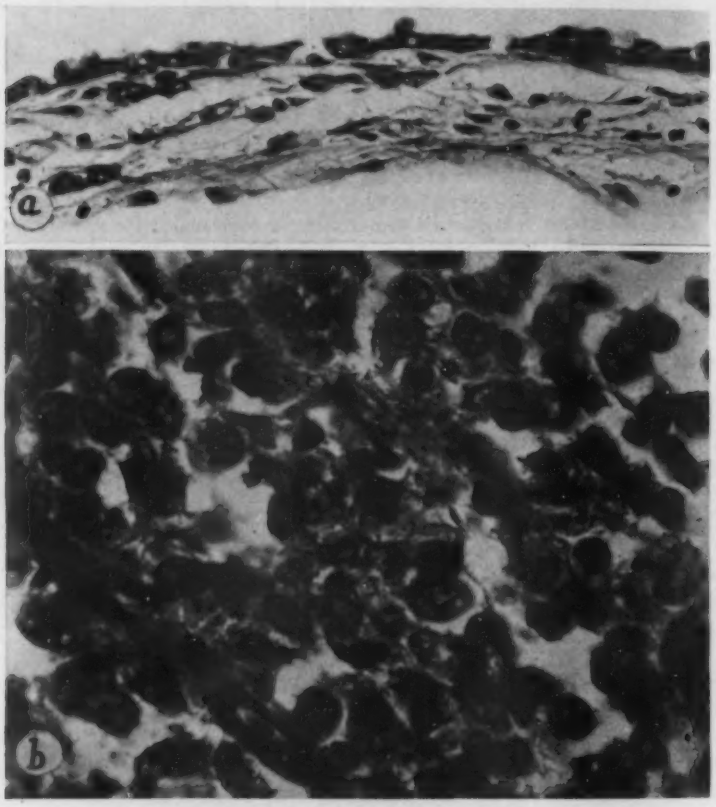

Fig. 2.—(*a*) Tumor cells "budding" from the arachnoid in the leptomeninges overlying the hippocampal gyrus (hematoxylin and eosin; × 300). (*b*) High power view of neoplastic cells. Note oval or polygonal shape, vesicular epithelial appearance and prominent nucleoli (hematoxylin and eosin; × 580).

distortion was much less marked. Above the level of the first thoracic vertebra and scattered throughout the leptomeninges in the cranial cavity were multiple small collections of tumor cells which again seemed to have arisen in many foci simultaneously rather than to have been produced by metastatic dissemination throughout the subarachnoid space against the direction of flow. These small nests of cells provided an excellent opportunity in many situations for a study of

the direct transformation from the adjacent normal arachnoid; from many such foci there were small extensions into the Virchow-Robin spaces along the cerebral fissures.

Histologic examination afforded an adequate explanation for the clinical phenomena noted. Weigert and Mallory-Heidenhain stains disclosed the lower half of the spinal cord to be distorted and almost completely destroyed; the funiculi were severely degenerated; cells of the anterior horn exhibited all grades of acute and chronic changes, and in the left lateral columns there was a large infarcted region of completely liquefied cord substance (fig. 3). Only mild changes in ganglion cells were in evidence in the brain, particularly in the hippocampus, area

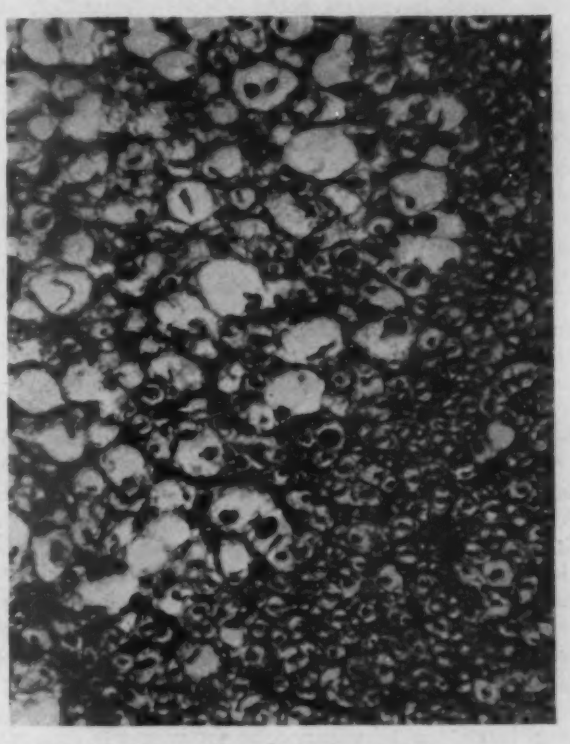

Fig. 3.—Zone of infarction and liquefaction in upper thoracic region of the spinal cord. Note the bullous axis-cylinders, swelling of the myelin sheaths and "varicosities" (Weigert; × 220).

striata and Purkinje cell layers, and appeared to be secondary to increased intracranial pressure. The anterior and posterior roots, as well as the nerves of the cauda equina, showed marked degeneration with considerable axonal damage and varying stages of swelling of myelin sheaths and droplet formation. In certain instances tumor cells had extended along the blood vessels into the epineural and perineural sheaths, and local circulatory obstruction had intensified the process. This "compression neuropathy" was likewise manifest in the peripheral trunks of the femoral and sciatic nerves bilaterally; less severe changes were observed in the brachial plexus. The internal hydrocephalus appeared to have resulted both from

tumor collections in the leptomeninges at the base of the brain, which interfered with the return circulation of cerebrospinal fluid to the villi of the convexity, and from obstruction to the outflow of fluid along the many perineural spaces of the spinal nerve roots.

COMMENT

The widespread involvement of the leptomeninges by tumor cells having morphologically benign characteristics immediately suggested that we were confronted in this case with something apart from the usual secondary infiltrative neoplasm. Thorough necropsy revealed no primary tumor in another situation and no solitary cerebral nodule from which such a spread could have originated. The obliteration of arachnoid landmarks revealed that in all likelihood this was a true "in situ" neoplasm, not remarkably different from multicentric "colloid" (mucus-forming) carcinoma of the stomach or multicentric carcinoma such as occasionally follows ulcerative colitis.

Globus [20] has pointed out the occurrence of a primitive meningeal anlage in neonatal life, particularly in association with congenital hydrocephalus. These rests resemble loose, amorphous sheets of cells which occupy the normal position of the leptomeninges. It seems likely that such malformations are compatible with life if they are not widespread enough to result in obstruction. Weinberger, as mentioned, regarded the condition in his case as originating in such an anlage; likewise, the embryologic character of the lesions in this case presupposes incomplete differentiation of the arachnoidal sheet of cells which had not been sufficient to block the cerebrospinal pathways. Conversion into tumor proceeded simultaneously in all sites, and only after two years (and doubtless longer) did compensation for this space-occupying lesion break down, with rapid progression of symptoms.

The diagnostic difficulties in cases of such rare diffuse meningeal tumors are obviously great. Looking at the problem in retrospect, we can say that the only clinical features of assistance are the evidence of disseminated involvement of the nervous system with a history suggesting "chronic meningitis" and a more recent exacerbation of the symptoms. Antemortem diagnosis depends on the demonstration of tumor cells in stained smears or paraffin-embedded sections of the sedimented spinal fluid. Rapid centrifuging so alters cellular appearance that identification is usually impossible. Even with excellent preparations the difficulty of distinguishing large mononuclear cells from small mononuclear cells which are present in numerous other types of chronic meningitic disease is by no means inconsiderable, particularly in the absence of mitotic figures. In this case the cell type would lead the pathologist to suspect that irradiation of the cerebrospinal axis might have offered considerable hope of palliation, but to our knowledge no similar tumor has been diagnosed in time to institute such therapy.

SUMMARY

A case of diffuse meningomatosis is reported, and its clinical and pathologic implications are discussed. The process resembles a neoplastic transformation of multicentric origin arising in an incompletely differentiated arachnoid membrane.

20. Globus, J. H.: Am. J. Dis. Child. **36**:680, 1928.

THYMOMA IN MYASTHENIA GRAVIS

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The association of myasthenia gravis and a tumor of the thymus gland was first described by Weigert in 1901. Since then 58 cases have been reported.

Myasthenia gravis is a chronic disease of adolescent and adult life characterized by a variable weakness of the voluntary muscles, usually first noted in the jaws and throat. The weakness varies in severity from day to day and may disappear for months or years, but the tendency of the disease is toward a sudden, unexpected fatal ending with respiratory failure.[1] The diagnosis is assured by two findings: (1) a prompt improvement in muscular function following the administration of prostigmine and (2) a perivascular lymphocytic infiltration observed in biopsy of a voluntary muscle (this has been termed a lymphorrhage).

A tumor of the thymus gland has been found in 50 per cent of those cases of myasthenia gravis in which postmortem examinations were made. In every instance the tumor was benign and predominantly epithelial. Cases of myasthenia gravis associated with thymoma have recently been reported by Norris,[2] Miller [3] and Blalock.[4]

REPORT OF A CASE

A 50 year old married man of Swedish descent was first admitted to the Evanston Hospital Sept. 25, 1938. His chief complaints were of weakness and early fatigue of the muscles of the jaw and throat, with resultant difficulty in chewing, swallowing and talking. This had begun fifteen months before admission and one month after apparent complete recovery from an attack of influenza. There was some improvement after the onset, but in the six months prior to admission the difficulty had become progressively worse. The symptoms were more disturbing when he was tired, and the best function was noted in the morning, after a night's rest. He had lost 13 pounds (5.9 Kg.) in weight since the onset, a loss which he attributed to difficulty in eating.

The past history was without bearing except for an attack of inflammatory rheumatism at the age of 27; on that occasion he was in bed two weeks. The family history was essentially noncontributory.

The patient was a thin, tall, well developed 50 year old white man, not acutely ill. There was slight difficulty in speech. The eyes, ears, nose and throat were

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1. Ironside, R.: Myasthenia Gravis, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1939, vol. 6, pt. 2, p. 998.

2. Norris, E. H.: (*a*) Am. J. Cancer **27**:421, 1936; (*b*) **30**:308, 1937.

3. Miller, H.: Arch. Path. **29**:212, 1940.

4. Blalock, A.; Mason, M.; Morgan, H., and Riven, S.: Ann. Surg. **110**: 544, 1939.

normal. The chest was clear to auscultation and percussion. A soft systolic murmur was heard over the cardiac apex. The rate, rhythm and borders were normal. The blood pressure was 136 systolic and 88 diastolic. Neurologic examination disclosed an early fatigue of the muscles of the jaw and eyelids, a fine tremor of the hands and a sluggish gag reflex. Roentgenologic examination of the esophagus and gastrointestinal tract gave no information as to the condition. No mention was made of any abnormality in the mediastinum.

The blood revealed hemoglobin 13 Gm. (84 per cent), red blood cells 4,500,000 and white blood cells 8,100. The Kahn test was negative. The urinalysis showed nothing of significance.

A diagnosis of myasthenia gravis was made, and a solution of prostigmine methyl sulfate (1.5 mg.) was administered hypodermically. The patient's response to this therapy was excellent and he was discharged with instructions to continue taking prostigmine bromide tablets by mouth.

Eleven months later he was readmitted in a dying condition, due to difficulty in breathing. He died four hours after admission despite administration of prostig-

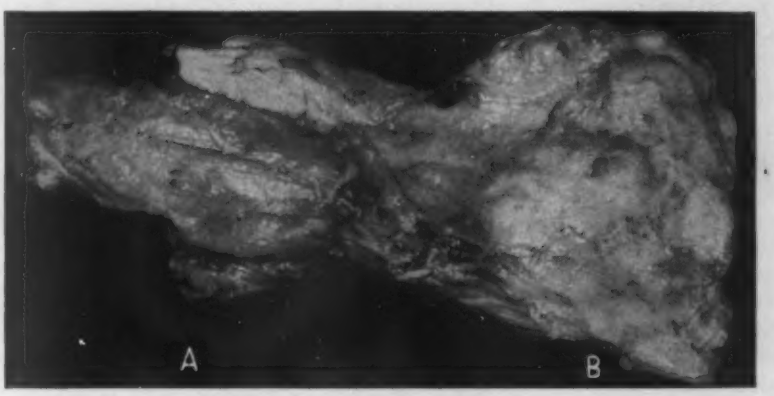

Fig. 1.—*A*, thymus; *B*, tumor; × 0.38.

mine and respiratory stimulants. The necropsy was made eight hours after death by Dr. E. L. Benjamin. Only the pertinent observations are given.

The body was that of a well developed, fairly well nourished 51 year old white man, 185 cm. long. The estimated body weight was 160 pounds (72.5 Kg.). The mouth was edentulous. The chest was symmetric but flat; the abdomen was scaphoid. The skin over the thoracic wall, arms, neck and face was tan. The right testis was atrophic. The midline fat was 5 mm. thick. The omentum and mesentery were atrophic. The skeletal muscle was grossly normal. The lungs were distended, and the mediastinal margin of the left upper pulmonary lobe was adherent to a tumor of the thymus.

The thymus and its tumor (fig. 1) weighed 93 Gm. The flat bilobed thymus was roughly triangular. The base was 5 cm. wide and the apex was 1.5 to 2 cm. wide. The gland was 1 cm. thick. Its caudal extremity merged with a firm to hard, pale gray-yellow pyramidal tumor, 5 by 5 by 1.5 to 2 cm. The tumor had a granular, slightly bosselated external surface. It was intimately attached to the pericardial sac beneath and laterally to the left upper pulmonary lobe.

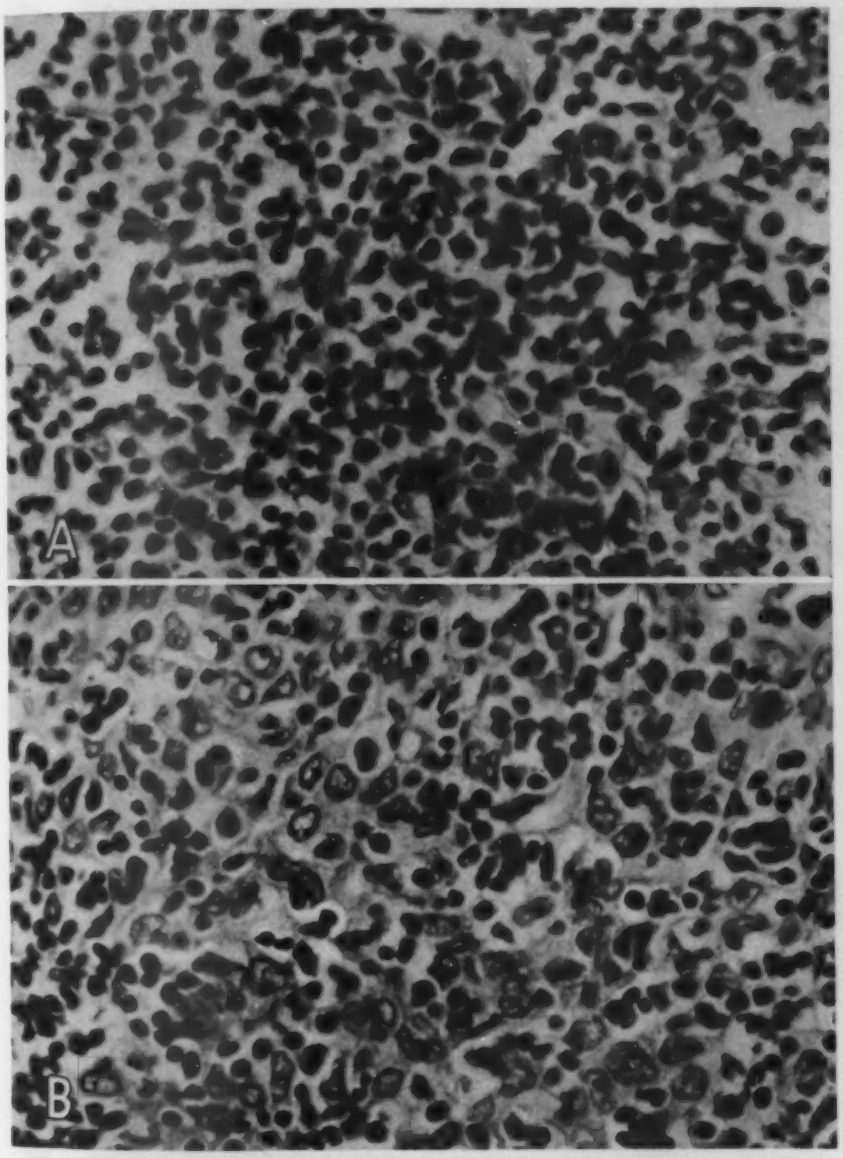

Fig. 2.—*A*, persistent thymus; *B*, tumor of thymus, showing diffuse hyperplasia of the epithelial cells and scattered small lymphocytes; × 590.

The thyroid gland weighed 49 Gm. and contained several small colloid fetal adenomas in the lower poles. The heart weighed 375 Gm. The mitral leaflets were shortened, and their margins were thickened along the line of apposition during closure. On the auricular surfaces of the valve leaflets was a zone of glistening verrucae, 6 mm. wide. The tricuspid valve was dilated. The right adrenal gland weighed 6 Gm. and the left 5 Gm. Their shape was normal. Cut surfaces revealed a pale gray medulla, 2 to 3 mm. wide. The zona reticularis was obscured. The zona fasciculata was 1 mm. wide.

Microscopic Description.—That part of the thymus gland uninvolved by the tumor (fig. 2 *A*) was composed of small irregular lobules separated by a fairly wide zone of fibrous stroma containing few fat cells and numerous engorged blood

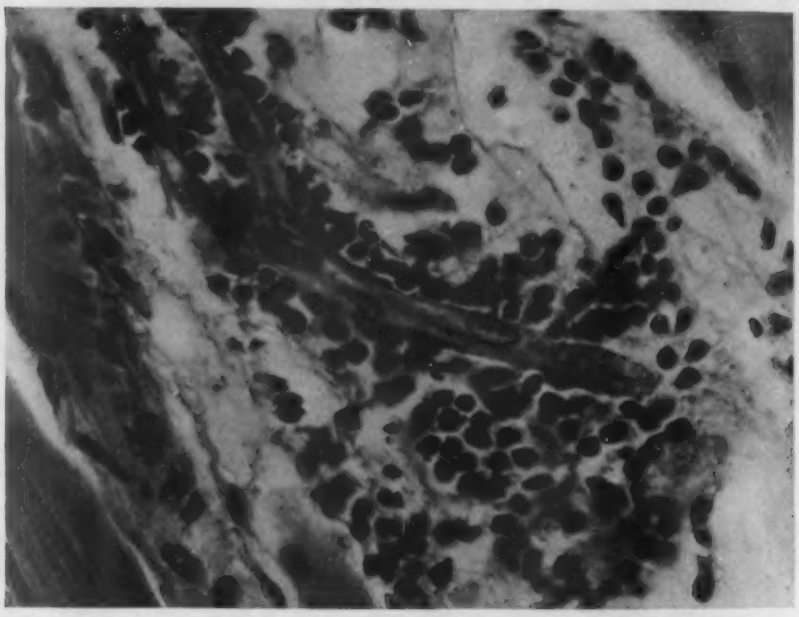

Fig. 3.—"Lymphorrhages" in skeletal striated muscle; × 550.

vessels. The capsule was indistinct. The numerous Hassall's corpuscles varied in structure. Some were young and composed of a condensation of large epithelial cells, forming compact bodies. The cells had an ample pale cytoplasm and a vesicular round nucleus. The peripheral portions of the lobules were formed by a scanty parenchyma of small basophilic lymphocytes with an occasional epithelial cell. As the thymus merged into the tumor (fig. 2 *B*) there presented large, hyperplastic irregular lobules, formed by proliferating epithelial cells, which occasionally produced immature structures resembling Hassall's corpuscles. The epithelial cells were large, the pink granular cytoplasm was abundant, and the large nucleus was composed of basophilic nuclear chromatin. Scattered throughout the delicate stroma were numerous small lymphocytes. In places the stroma became compact to form thick trabeculae which supported capillaries, arterioles, venules, veins and arteries. In places the stroma had undergone a pale pink granular degeneration.

In the diaphragm the striated muscle was well preserved. No significant round cell infiltration was present. Four of eight sections from the skeletal muscle displayed considerable perivascular infiltration of small and medium-sized round cells (lymphorrhages) (fig. 3). The seminiferous tubules of the testis were atrophic. There was moderate hyperplasia of the interstitial cells.

COMMENT

The case presented serves as further evidence that a relation exists between myasthenia gravis and the thymus gland. Microscopic sections of the thymic tumor reveal a benign epithelial hyperplasia which is similar to that in the microscopic sections in other reported cases. Small tumors of the thymus might easily be overlooked in necropsies of patients with myasthenia gravis. Norris in his review [2a] stated that one tumor reported by Link (1902) was only 3 cm. long and that another reported by Dupré and Pagniez (1905) weighed 8 Gm. Norris stated that pathologic changes may be found in the thymus in cases of myasthenia gravis in direct ratio to the care with which they are sought.

An attractive assumption is as follows: The epithelial cells of the thymoma liberate a hormone which acts at the myoneural junction by rapid destruction of acetylcholine; i. e., the hormone's action is the opposite of that of prostigmine. This results in (1) an early fatigue of the voluntary muscle, hence the symptoms of myasthenia gravis, (2) the usual reaction of round cell infiltration in the muscle (the lymphorrhage) and (3) eventual loss of response at the myoneural junction, leading to death from failure of the respiratory muscles.

Experiments with an extract of one of these tumors known to have been associated with myasthenia gravis, as suggested by Miller,[3] might prove this supposition to be true.

SUMMARY

A case of myasthenia gravis is reported in which a tumor of the thymus gland was found at necropsy. This brings the reported cases of this association to 59. In 50 per cent of the reported cases of myasthenia gravis there has been an associated neoplasm of the thymus gland. The supposition that the epithelial cells liberate a hormone remains to be proved.

Forensic Medicine

POSTMORTEM DIAGNOSIS OF ALLERGIC SHOCK

THE VALUE OF THE PRAUSNITZ-KÜSTNER REACTION

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AND
ERNEST L. HUNT, M.D.
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Although the diagnosis of allergy is ordinarily a clinical problem, there are occasions on which proof of specific hypersensitivity is desirable at postmortem examination. Such evidence is especially desirable if the death has occurred suddenly and under circumstances which suggest that allergic shock may have been the cause. Under these circumstances the acquisition of objective evidence of the presence of specific allergic reactivity is likely to be medicolegal as well as of scientific interest.

To establish a diagnosis of hypersensitivity after death, advantage may be taken of the fact that the blood serum in allergic disease frequently has specific characteristics which are readily demonstrable by passive sensitization of normal living tissue. With the exception of drug idiosyncrasy the various forms of hypersensitivity which are attended by the hazard of a fatal reaction may be demonstrated by this means. Since it appears likely that the different types of hyperreactivity depend on different mechanisms of sensitization and since there are individual differences in the application of diagnostic tests, the atopic and immune groups will be discussed separately.

PASSIVE TRANSFER OF ATOPIC HYPERSENSITIVITY

The hypersensitivity in this group is thought to be due to the presence in the body of a specific sensitizing agent called reagin, the development of which probably depends on a hereditary constitutional abnormality (Coca [1]). Atopic reactions include a variety of disorders, among which are hay fever, asthma, eczema, gastrointestinal disturbances and migraine. From the standpoint of sudden death in man, especially

From the Department of Legal Medicine, Harvard Medical School, and the Office of the Associate Medical Examiner of the Eleventh District of Worcester County of the Commonwealth of Massachusetts.

1. Coca, A. F.: Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **14**:538, 1933.

that resulting from the injection of a foreign protein, this is the most important type of hypersensitivity.

Reagin differs from the immune antibodies in its failure to "neutralize," precipitate or agglutinate antigen, in its comparative thermal lability and in the marked degree of its local tissue fixation (Coca and Grove [2]; Levine and Coca [3]; Gay and Chant [4]; Cooke and Spain [5]; Loveless [6]).

The effects of passive sensitization through the transfer of reagin were first noted by Ramirez [7] in 1920. He reported a case in which the transfusion of blood from an asthmatic person to a nonallergic person induced asthma of the same etiologic type as that of the donor. Similar accidental cases were subsequently reported. In 1921 Prausnitz and Küstner [8] demonstrated that injection of the serum of a naturally allergic person into the skin of a normal person caused a specific local hypersensitivity. This reaction has proved to be a convenient diagnostic procedure.

Atopy appears to be confined to human beings, and the transfer of reagin to lower animals fails to induce passive anaphylaxis or the Schultz-Dale phenomenon of smooth muscle contraction (Cooke and Spain [5]). However, a state of local cutaneous hypersensitivity has been induced in certain apes and monkeys (Caulfield, Brown and Waters [9]; Straus [10]).

PASSIVE TRANSFER OF IMMUNE HYPERSENSITIVITY

This form of hypersensitivity is associated with the mechanism of infection and immunity and is manifested in man by bacterial allergy and induced sensitivity to foreign protein (e. g., serum sickness). The altered reactivity of persons in this group and the ability to induce sensitization of normal tissues by the technic of passive transfer are taught to depend on the presence of antibodies in the immune serum.

The first observations on the transfer of immune hypersensitivity were made in 1907 (Nicolle [11]; Gay and Southard [12]; Richet [13]; Otto [14];

2. Coca, A. F., and Grove, E. F.: J. Immunol. **10**:445, 1925.
3. Levine, P., and Coca, A. F.: J. Immunol. **11**:411, 1926.
4. Gay, L. N., and Chant, E. C.: Bull. Johns Hopkins Hosp. **40**:270, 1927.
5. Cooke, R. A., and Spain, W. C.: J. Immunol. **17**:295, 1929.
6. Loveless, M. H.: J. Immunol. **38**:25, 1940.
7. Ramirez, M. A.: New York State J. Med. **112**:115, 1920.
8. Prausnitz, C., and Küstner, H.: Centralbl. f. Bakt. (abt. 1) **86**:160, 1921.
9. Caulfield, A. H. W.; Brown, M. H., and Waters, E. T.: Proc. Soc. Exper. Biol. & Med. **35**:109, 1936.
10. Straus, H. W.: J. Immunol. **32**:251, 1937.
11. Nicolle, M.: Ann. Inst. Pasteur **21**:128, 1907.
12. Gay, F. P., and Southard, E. E.: J. M. Research **16**:143, 1907.
13. Richet, C.: Ann. Inst. Pasteur **21**:497, 1907.
14. Otto, R.: München. med. Wchnschr. **54**:1665, 1907.

Friedemann [15]), and most subsequent investigations have been made on experimental animals. Hypersensitivity has been produced by transfers of reactive immune serum from one animal to another in the same species and in some instances by transfer of such serum to animals of other species.

Immune hypersensitivity in man, with the exception of the tuberculin type of reaction, can be demonstrated by homologous local passive cutaneous sensitization in a manner similar to that used in demonstrating the atopic state. In addition, however, and in contrast to atopic sensitivity, it can be successfully transferred from man to certain of the lower animals (Novotny and Schick [16]; Grysez and Bernard [17]; Anderson and Frost,[18] and others), inducing passive anaphylaxis or the contraction of isolated smooth muscle (Schultz-Dale phenomenon). Of these procedures, homologous cutaneous sensitization is more likely to yield satisfactory results (Cooke and Spain [5]).

A CASE IN WHICH PASSIVE TRANSFER OF REAGIN WAS USED AS A MEDICOLEGAL TECHNIC

The value of applying the technic of local passive sensitization in the investigation of clinical and experimental problems has long been recognized. The following case is, so far as we know, the first one in which the passive transfer test has been utilized to establish a diagnosis of allergy at autopsy.

On Aug. 27, 1940, a case of sudden death became the subject of a medicolegal investigation.

The deceased person was a white woman 21 years of age who had been employed as a ward maid in a hospital. She had volunteered to serve as a control subject in an investigation in which a series of normal and psychopathic persons were receiving intracutaneous injections of small amounts of guinea pig hemoglobin. At 9:09 a. m. August 27 she received 0.2 cc. of a solution of guinea pig hemoglobin intracutaneously. She was but one of many volunteers to be given such an injection that morning. Within a few minutes after receiving the injection she complained of headache, suffered from respiratory distress, began to wheeze and became intensely cyanotic. She was given one subcutaneous and three intracardiac injections of epinephrine hydrochloride without avail. She was pronounced dead at 9:25 a. m.

All of the volunteer control subjects in the investigation had been interrogated concerning past illnesses and particularly concerning allergy. The woman who died had withheld the information that she had heart disease and asthma.

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15. Friedemann, U.: München. med. Wchnschr. **54**:2414, 1907.

16. Novotny, J., and Schick, B.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:671, 1909.

17. Grysez, V., and Bernard, A.: Compt. rend. Soc. de biol. **73**:387, 1912.

18. Anderson, J. F., and Frost, W. H.: Studies upon Anaphylaxis with Special Reference to the Antibodies Concerned, Hygienic Laboratory Bulletin 64, United States Treasury Department, Public Health Service, 1910.

At the time of the autopsy, no information was available as to any antecedent contacts that the woman might have had with guinea pigs, and no information had been obtained concerning the occurrence of allergy in her family.

The following information was later obtained from the mother of the dead woman and from physicians whose patient she had been.

She had suffered from asthma for eight years and had showed positive cutaneous reactions to dog hair, kapok, shellfish, ragweed, timothy, orris root and house dust. Negative results were obtained with egg, milk, rabbit hair and chicken feathers. To the mother's knowledge, the subject had never had any contact with guinea pigs. She had had symptoms in childhood which suggested rheumatic fever or infantile paralysis to her attending physicians. She had physical signs of mitral stenosis, but there was no record of cardiac decompensation.

The family history of this woman is extremely interesting. Her mother had asthmatic attacks and also had had symptoms of hay fever during one summer. A daughter of a sister of the maternal grandmother at the age of 17 died in convulsions within ten minutes after a subcutaneous injection of diphtheria antitoxin. Inasmuch as the symptoms of diphtheria had been mild, it was apparent that the administration of serum was responsible for the fatality, and the case gained considerable notoriety in the lay and the medical press. This occurred in 1895, when the concept of allergy and of anaphylaxis was still unknown to the medical profession, and it was the first case of death due to serum therapy to be reported in this country (Kortright [19]; Report of the American Pediatric Society [20]).

Autopsy.—The postmortem examination was begun six and one half hours after death and was performed by Dr. Alan R. Moritz, Dr. Ernest L. Hunt and Dr. Herbert Lund.

The body was that of a well developed, well nourished white woman. Rigor mortis was incomplete, and there was marked lividity of the dependent parts of the body.

On the volar aspect of the right forearm there was an area of dark red discoloration, measuring 4.0 by 2.5 cm. Within it there was a zone of intense dark blue discoloration, measuring 1 cm. in diameter, in the center of which a needle puncture wound could be identified.

The mucosa lining the air passages from the pharynx to the small bronchi appeared edematous and hyperemic. The swelling was most pronounced in the larynx, in the region of the arytenoid folds. Masses of mucus were present in the upper air passages. Microscopically, there was intense capillary congestion, and in addition to collections of fibrin neutrophilic and eosinophilic leukocytes were scattered through the interstitial spaces of the mucous membrane. In the outer portions of the walls of the air passages there were focal areas of hemorrhage.

The lungs were irregularly distended and overlapped in the midline after the sternum was removed. Although they did not collapse when the large air passages were opened, they did collapse when the various lobes were sectioned. There was a single large pedunculated multilocular emphysematous bulla attached to the anteroinferior margin of the lower lobe of the right lung. Otherwise the

19. Kortright, J. L.: Brooklyn M. J. **10**:86, 1896.

20. Report of the American Pediatric Society's Collective Investigation into the Use of Antitoxin in the Treatment of Diphtheria in Private Practice, J. A. M. A. **27**:27, 1896.

lungs showed no disturbance in structure. The cut surfaces were pale and dry. Plugs of mucus were identified in many of the smaller bronchi. Microscopically, the bronchial mucosa was edematous and sparsely infiltrated by neutrophilic and eosinophilic leukocytes. There was an excessive amount of mucus, which in places appeared to be obstructive. Many of the smallest bronchioles were greatly distended. The walls of the small arteries appeared to be thicker than usual, and moderately pronounced intimal hyperplasia was recognized in many of the arterioles.

The heart weighed 260 Gm. and apart from moderate dilatation of the right auricle showed no abnormality on external examination. The walls of none of the chambers appeared hypertrophic, and with the exception of a slight amount of fibrosis in the region of the mitral ring the myocardium appeared normal. The leaflets of the mitral, aortic and tricuspid valves showed fine verrucous irregularities near the free margins. The circumference of the mitral orifice was reduced to 7 cm., and the chordae tendineae of the shorter leaflet were thickened and adherent to one another. There was no significant deformity of the aortic or tricuspid valves. On the posterior surface of the left auricle there were a number of smooth gray confluent sessile plaques of endocardial thickening. The aorta was slender and its wall thin. The circumference of the aorta in the ascending portion of its arch was 5.5 cm. Many sections from various portions of the heart failed to disclose Aschoff's nodules, and with the exception of a few scattered mononuclear cells in the posterior leaflet of the mitral valve there was no evidence of active inflammation.

The remainder of the postmortem examination failed to disclose any significant pathologic changes.

Despite the fact that sensitivity to guinea pig protein is not common and that the dose given the deceased had been extremely small, it was felt that the most tenable explanation of her fatal collapse was allergic shock. Although it is possible that inflammation of the respiratory passages and chronic rheumatic heart disease may have contributed to her death, they did not in themselves provide an adequate explanation. It seemed highly desirable in the elucidation of the case to demonstrate whether or not there was in the blood of the deceased a specific reagin to guinea pig hemoglobin. It was therefore decided to employ the technic of local passive sensitization to investigate this possibility.

Passive Transfer Test.—About 20 cc. of the dead woman's blood was taken by aseptic technic from the right auricle. The serum was separated from the clot and stored in the refrigerator. Seven days later several intracutaneous injections of 0.1 cc. of this serum were made in widely separated sites on the volar aspects of the forearms of each of three persons. Twenty-four hours later one or more of the injected sites on each person were tested for sensitivity to guinea pig protein. Light superficial scratches were made, and after a lapse of fifteen minutes a small amount of fresh guinea pig blood was smeared over the scratches. This was allowed to dry and then was laked with a little sterile distilled water and allowed to dry again. Within eight minutes after the application of the guinea pig blood, two of the recipient noticed itching at the site of the test. A flare and wheal appeared at this time in subject 1. A flare was noticed in thirteen minutes and a wheal in eighteen minutes in subject 2. The

reactions reached maximum intensity in about thirty minutes. The reaction in subject 1 was the more marked, the flare being 4.5 cm. and the wheal 1.1 cm. in diameter. In the skin reaction in subject 2 the flare was 3 cm. and the wheal 0.8 cm. in diameter. In about one hour the reactions began to fade and in two and a half hours they were very faint. Subject 3 showed no reaction.

At the time of the injection of the test serum, serum from a nonallergic control subject had been injected into the skin of each of the three persons. Scratch tests with guinea pig blood were made in these areas and also on areas of untreated skin. There was no reaction in these control areas.

The test was repeated on subject 1 forty-eight hours after the original injection, with similar positive results.

The fact that subject 3 did not react to the serum does not detract from the validity of the positive reactions of subjects 1 and 2, for it has been shown that about 11 per cent of normal persons are nonreactive (Coca and Grove [2]).

The reactions of subjects 1 and 2 were clearcut and adequately controlled, and were accepted as positive evidence of the presence of a reagin specific for some component of guinea pig blood.

Certain additional tests were made at a later date on subject 1, commercial powdered allergens being used. Dog hair evoked a positive reaction. To mixed duck, chicken and goose feathers there was no response. Horse dander caused no reaction.

COMMENT

A summary of the evidence in this case shows that a diagnosis of allergic shock is justified:

The injected material was not toxic to a normal person.

The symptoms produced were characteristic of an allergic reaction.

The autopsy disclosed no other explanation of death.

A specific sensitizing agent corresponding with the material injected was found in the blood serum by the technic of passive transfer.

The case contributes further information of academic interest. The anaphylactic death of the mother's cousin and the asthma and hay fever in the mother indicate the presence of hereditary hypersensitivity. The fact that the deceased had no known contact with guinea pigs seems to indicate that the development of hypersensitivity of the hereditary type does not necessarily require antecedent contact with the specific exciting substance. These facts add further support to the recognition of atopic persons as a distinct group in which a hereditary abnormality is the essential factor in the development of hypersensitivity and exposure to the exciting substance is of secondary importance.

SUMMARY

The demonstration at postmortem examination of hypersensitivity to a specific allergen is possible by means of the passive transfer technic. The value of this procedure has been shown by the report of a case of fatal allergic shock.

General Reviews

GENERAL PATHOLOGY AND SOME SPECIAL COMPLICATIONS OF ALCOHOLISM

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Of the many phases of the problem of alcoholism, that which is concerned with the general pathologic effects of alcohol on the body has lent itself least easily to morphologic and experimental investigation. In general, alcoholism per se is not an adequate cause of death unless, as is fortunately uncommonly the case, an extreme overdose is taken, sometimes by an adult or, usually accidentally or unwittingly, by a child. Except for these rare cases in which an overdose of alcohol is taken by an inexperienced drinker, the majority of cases of acute alcoholism are those of persons suffering from chronic alcoholism. Acute alcoholism, as Loeb [1] observed, is usually only an episode in the picture of the chronic alcoholic state. Death of such persons, if and when it occurs, is nearly always due less to acute alcoholic intoxication than to some complication, such as severe trauma, suffocation from aspirated food or regurgitated gastric contents, chronic vitamin deficiency or an intercurrent infection, e. g., pneumonia. Nevertheless, certain pathologic changes, usually mild, have been found to be commonly present in the bodies of persons who have died primarily as a result of acute alcoholic intoxication. Even though they are not specific or pathognomonic, they will be described briefly.

The general examination of the body of the victim of acute alcoholic poisoning reveals surprisingly little. The changes most commonly seen are in the stomach and the brain. Even in these organs they may not be marked, and by some observers, notably Martland,[2] they have not been found at all in some cases.

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1. Loeb, W. A.: M. Bull. Vet. Admin. **16**:258, 1940.

2. Martland, H. S.: The Pathology of Acute and Chronic Alcoholism, in Emerson, H.: Alcohol and Man, New York, The Macmillan Company, 1935, pp. 201-223.

In the stomach, as many observers, notably Welch,[3] Hirsch[4] and Martland,[2] have pointed out, there are hyperemia of the mucous membrane, sometimes minute petechial mucosal hemorrhages and sometimes actual, though very small, superficial mucosal erosions or ulcerations, found most commonly near the pyloric end of the organ. Lesions do not occur in the mouth, on the tongue or in the pharynx or esophagus. The tongue may be coated and the buccal mucous membrane pale, but such changes are common in any form of gastrointestinal upset.

Examination of the contents of the stomach may yield helpful data, since some recognizable alcoholic beverage may be detected; if not, the presence of alcohol may be demonstrated by chemical analysis. The finding of alcohol, especially if in considerable quantities, in the stomach of a person apparently dead in a drinking debauch, is significant. Nevertheless, as medical examiners well know, such a finding must be interpreted with great care, especially if traumatic injuries are also present. Attempts have been made to hide manslaughter or murder beneath the cloak of apparent alcoholic intoxication of the unfortunate victim. Large amounts of an alcoholic beverage have actually been introduced into the stomach after death in the hope of deceiving the examiner. However, the postmortem introduction of a beverage can be readily detected.

The remaining portions of the intestinal tract usually show no changes of note. Traces of alcohol may be found in the intestine, but hyperemia may be absent and ulceration is rarely observed.

The liver may show no changes or may appear moderately congested. Sometimes it has been found to be unusually pale and fatty, but fatty changes are not characteristic of uncomplicated acute alcoholic intoxication.

Pulmonary changes, such as edema, general congestion and focal hemorrhages, are common. More often than not, these changes in the lungs are apt to be only indirectly the result of alcoholism. The trachea, bronchi and often the smaller branches of the bronchial tree may contain much frothy pinkish fluid with which are mixed alcoholic beverages or regurgitated gastric contents. In the presence of this complication, death may be the result of suffocation. In this case postmortem lividity is usually marked; the heart, especially the right auricle and ventricle, is dilated and filled with dark red unclotted blood; small petechial hemorrhages are found on many serous surfaces, notably those of the pleural and pericardial cavities. These changes, however, are commonly found in association with suffocation from any cause. They are not due to alcoholism alone.

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3. Welch, W. H.: The Pathological Effects of Alcohol, in Atwater, W. O.; Billings, J. S.; Bowditch, H. P.; Chittenden, R. H., and Welch, W. H.: Physiological Aspects of the Liquor Problem, Boston, Houghton, Mifflin & Co., 1903, vol. 2, pp. 349-374.

4. Hirsch, E. F.: Arch. Int. Med. **16**:354, 1916.

The kidneys may appear normal, or if the dead person has been engaged in a prolonged drinking bout, may appear congested and edematous, often with rather marked cloudy swelling.

In the brain the changes, as we have noted, are definite, although when one considers the magnitude of the clinical manifestations, they seem mild and insignificant by comparison. The subarachnoid space over all portions of the organ is edematous, often being so full of fluid that the surfaces are dripping wet. When the dura is elevated, clear cerebrospinal fluid may flow freely from the space beneath, often as much as 10 to 40 cc. escaping. Congestion of the superficial vessels, usually veins, is slight, though almost universally present. The brain itself is heavier than usual and, like the meninges, is edematous and often slightly to moderately congested. Except for these changes, there is little else to be found morphologically. Even careful microscopic examination fails to disclose any typical, characteristic or universally present alterations of the cerebral tissues or the nerve cells.

The term "chronic alcoholism," as Loeb [1] aptly observed, should be used only with reference to the pathologic, not the social, drinker, in spite of the difficulty of defining with any degree of exactness where "social" drinking terminates and "pathologic" imbibing begins. In this discussion I wish to consider only the pathologic drinker. Moreover, it should be remembered that most of those who die in an acutely intoxicated state are persons suffering from chronic alcoholism in whom the acute state is merely an episode in the general picture of chronic alcoholism. Thus, in these persons the changes of acute alcoholism are grafted on those which, even though not striking or uniformly present, may be said to characterize the chronic alcoholic state.

The term "chronic consumer of alcoholic beverages" is difficult to define specifically. It is used here to refer to the drinker who imbibes frequently such quantities of alcoholic liquors that he maintains a sufficiently high concentration of alcohol in the blood and tissue fluids to keep him constantly or for long periods at a time under some degree of the influence of alcohol. There are those who may be considered to suffer from moderate chronic alcoholism, who abstain from time to time. Others, hardened veterans of the bottle, are never without their beverage. Their tissues may be said to be perpetually "soaked" in alcohol. Among these are the unfortunate ones who suffer from the complications that result from faulty nutrition, especially from the lack of adequate amounts of certain of the vitamins. Some of these patients, however, partly as a result of sedentary habits and the resultant lack of exercise, partly because of an increased intake of food with excessive storage of fat, become obese. The obesity, however, is not a direct result of chronic alcoholism. It is an associated state, more common in the "heavy beer

drinker" than in the partaker of "hard liquor" and often seen in the lazy, gluttonous nondrinker as well.

There are certain persons with moderate chronic alcoholism, on the other hand, who work hard, exercise repeatedly, eat wisely and try, in spite of their alcoholic addiction, to keep physically fit. These are the persons who are said by some, notably Leary [5] and Martland,[2] to show less arteriosclerosis, less evidence of hypertension, fewer attacks of gallstones and fewer other organic changes than do nondrinkers of the same age group. Eberhard [6] showed experimentally that in rabbits at least the deposition of cholesterol in the aorta and liver is definitely less pronounced when alcohol is fed with the cholesterol than when cholesterol is given alone. It is not possible at the present time to confirm the contention that, because alcohol may be a factor in preventing the precipitation of cholesterol and its esters, it may also prevent the early production of atherosclerosis. Interest in this aspect of the possible effect of alcohol, however, seems to be growing.

The pathologic changes of chronic alcoholism in the gastrointestinal tract, though not striking, are well known and have been described in detail by many pathologists, notably Welch [3] and Martland.[2] Briefly, they consist of a mild chronic catarrhal inflammation, which affects especially the gastric mucosa. This condition is in no way characteristic of alcoholic intoxication alone. It can be produced by any toxic or irritating substance taken by mouth over varying periods. The changes may be somewhat more marked in those who drink liquors of high alcoholic content or who take alcohol frequently on an empty stomach. In such persons there may also be present in the stomach increased amounts of mucus, probably produced as a result of the undue irritation of the mucosa. In habitual drinkers, indeed, as Boyd [7] pointed out, the chronic gastritis may become in time sufficiently severe to be associated with definite atrophy of the gastric glands and consequent diminution in the production of hydrochloric acid. This change, however, is late.

Though there is a prevalent notion that these organic gastric changes may predispose to chronic peptic ulcer and carcinoma, there is no convincing evidence in favor of such a relationship. Moreover, all authorities agree that alcohol can in no sense be considered a cause of cancer. There are some who believe that the superficial erosions which may result from acute alcoholic injury of the gastric mucous membrane may provide the initial lesion on which a peptic ulcer can develop, but the incidence of peptic ulcer appears not to be any higher in habitual

5. Leary, T.: New England J. Med. **205**:231, 1931.

6. Eberhard, T. P.: Arch. Path. **21**:616, 1936.

7. Boyd, W.: The Pathology of Internal Diseases, ed. 3, Philadelphia, Lea & Febiger, 1940, p. 265.

drinkers than in abstainers. In the experience of Martland [2] peptic ulcer has occurred less frequently in patients with alcoholism than in nondrinkers.

In the intestine there are usually no lesions which can be attributed to alcohol except, perhaps, a mild, superficial, low grade chronic inflammation of the mucous membrane. In their study of a series of persons treated for alcoholism at the Lakeside Hospital in Cleveland, Richardson and Blankenhorn [8] found conspicuous symptoms so infrequently that they stated quite frankly that they were "amazed, in contemplating this group, by the enormous amounts of alcohol consumed and the scanty signs of injury therefrom."

Pathologic changes in the liver have been the source of much discussion and debate. For years the picture of the gin drinker's liver, showing alcoholic (or atrophic) cirrhosis, has been held forth as demonstrating the terrible price the victim of excessive inebriation paid for his folly. Mallory [9] described the lesion in detail and he, Welch,[3] McJunkin [10] and others have felt that in spite of the fact that abstainers as well as chronic drinkers of alcohol may suffer from this type of cirrhosis, alcohol may, if only indirectly, play some part in the development of the lesion.

In general, however, experimental evidence in favor of a direct relation between chronic alcoholism and cirrhosis has been difficult to obtain. Many investigators have attempted to produce cirrhosis in animals by giving alcohol, even in large quantities, all to no avail. Moon [11] in a review of the work in this field made clear the degree of failure which has attended the great variety of experiments which have been carried out. From the experimental side, therefore, at least until very recently, it has not been possible to show that alcohol played any direct role in the production of atrophic cirrhosis in animals.

The suggestion has been made that some ingredient or impurity present in alcoholic beverages might have been hepatotoxic and therefore responsible for the production of the cirrhosis. It is well known that various toxic substances, notably copper, arsenic, chloroform, carbon tetrachloride, phosphorus and cinchophen, can produce hepatic injury which may finally terminate in cirrhosis. Might not one of these agents or some as yet unknown but similarly toxic impurity in the alcoholic beverage be the actual unknown substance? This is admittedly possible. Bollman and Mann [12] added alcoholism to phosphorus poisoning and found a marked enhancement of the damaging effect of phosphorus on

8. Richardson, J. L., and Blankenhorn, M. A.: Am. J. M. Sc. **176**:168, 1928.
9. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.
10. McJunkin, F. A.: Arch. Int. Med. **19**:787, 1917.
11. Moon, V. H.: Arch. Path. **18**:381, 1934.
12. Bollman, J. L., and Mann, F. C.: Ergebn. d. Physiol. **38**:445, 1936.

the liver. Lamson and Wing [13] similarly found that alcoholism added to carbon tetrachloride poisoning increased the severity of the effect of pure carbon tetrachloride on the liver. Thus alcohol when combined with certain other agents has greatly increased their toxic effect on the liver.

Recently, however, the first promising experimental studies have been reported. Connor and his colleagues [14] have been able, by the giving of pure ethyl alcohol, to produce in dogs and rabbits a condition resembling alcoholic (or atrophic) cirrhosis in man. Briefly, these workers first noted that some patients with diabetes and depancreatized dogs showed a form of cirrhosis of the liver which was indistinguishable from that found in chronic alcoholism in man. In each case fatty infiltration of the liver was marked. In the diabetic dogs, which were fed adequate diets and insulin, cirrhosis developed in two and six-tenths to five and five-tenths years. The earliest hepatic change, however, was the marked fatty infiltration which occurred as early as twenty weeks after pancreatectomy and persisted for long periods. Hyaline degeneration of many liver cells followed and ultimately cirrhosis. The scarring was believed to develop in response to the presence of large amounts of fat within the liver cells.

These observations led to an inquiry into the nutrition and possible biochemical states of patients addicted to the consumption of alcohol. It was felt that in alcoholism there might be "internal starvation, as there is in diabetes, due to the inability of the tissues to utilize sugar and other food substances." It was noted, too, that actual or partial starvation frequently occurred in drunkards and that when food was eaten it consisted largely of fats and proteins, not carbohydrates.

In their experiments with alcohol, these workers fed normal dogs and rabbits on a high fat, high protein diet with adequate vitamins and minerals. They then administered alcohol by mouth, the amounts varying but being quite high, often in the neighborhood of 10 cc. of 20 or 22.5 per cent alcohol per kilogram of body weight, twice a day. In all animals studied they found marked fatty infiltration of the liver similar to that seen frequently in severe chronic alcoholism in man. This was considered to be the important lesion which preceded cirrhosis. In many animals this change was accompanied or followed by atrophy of the hepatic cells, most commonly at the periphery of each affected lobule. Many of these atrophic cells showed hyaline degeneration, sometimes with actual necrosis, similar to that observed and first described by

13. Lamson, P. D., and Wing, R.: J. Pharmacol. & Exper. Therap. **29**:191, 1926.

14. Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Am. J. Path. **14**:101, 1938. Connor, C. L.: ibid. **14**:347, 1938. Connor, C. L., and Chaikoff, I. L.: Proc. Soc. Exper. Biol. & Med. **39**:356, 1938. Connor, C. L.: Arch. Path. **30**: 165, 1940; Quart. J. Stud. Alcohol **1**:95, 1940.

Mallory [9] in the liver in alcoholic cirrhosis in man. Finally, in a number of animals actual cirrhosis, situated in the perilobular or portal regions, was found, usually moderate in degree but definite and clearcut. The character of the cirrhosis, moreover, differed from that which they [15] were able to produce in normal dogs by the feeding of high fat diets alone. It thus appears that in dogs and rabbits pure alcohol acting on a markedly fatty liver can produce a form of cirrhosis of the liver which resembles so-called alcoholic cirrhosis in man.

That a dietary deficiency alone, totally apart from any ingestion of alcohol, may also play some role in the production of cirrhosis is indicated by the recent work of Rich and Hamilton,[16] who produced in rabbits a form of cirrhosis resembling the alcoholic, or Laennec, type in man by feeding diets supplemented by various vitamins but lacking yeast. Patek,[17] moreover, reported beneficial results in the treatment of malnourished, chronically alcoholic patients with alcoholic cirrhosis of the liver by the giving of a diet high in vitamin content, especially in vitamin B complex. The livers in 10 of 13 patients were reduced in size, ascites was diminished, and many associated conditions, such as peripheral neuritis, dermatitis and glossitis, cleared up. Patek considered that there was a possible relation between a nutritional deficiency and alcoholic cirrhosis. Goodhart and Jolliffe,[18] while treating alcoholic addicts for polyneuritis with vitamin B_1, found that in 1 patient with cirrhosis of the liver a remission of this condition was produced. At the time of their report the remission had lasted more than eleven months.

There is, therefore, no sound reason, in the light of the experimental work which has recently been reported, to exclude alcohol as one cause of hepatic cirrhosis. The experiments of Connor and co-workers indicate quite clearly that alcohol can exert a direct action on the liver cell once the cell is filled with fat. Since animals used by these workers were given fat diets which contained adequate amounts of vitamins as well as minerals, it may be assumed that a concomitant food deficiency did not exist. Nevertheless, in view of Rich and Hamilton's experimental studies and the clinical observations of others, the possibility that cirrhosis of the liver, like polyneuritis, may sometimes be due in part to associated avitaminosis must still be borne in mind.

From the standpoint of clinical experience alone, as reported by many workers, alcoholism is perhaps the most common single clinical condition which is associated with cirrhosis, some 50 to 60 per cent of patients with cirrhosis having chronic alcoholism. From 5 to 8 per cent

15. Chaikoff, I. L., and Connor, C. L.: Proc. Soc. Exper. Biol. & Med. **43**: 638, 1940.

16. Rich, A. R., and Hamilton, J. D.: Bull. Johns Hopkins Hosp. **66**:185, 1940.

17. Patek, A. J., Jr.: Proc. Soc. Exper. Biol. & Med. **37**:329, 1937.

18. Goodhart, R., and Jolliffe, N.: J. A. M. A. **110**:414, 1938.

of all alcoholic addicts have cirrhosis, and the condition occurs much less frequently in abstainers than in addicts. Moreover, as Martland [2] stated, the prevalence of cirrhosis has varied quite consistently in modern nations with the consumption of alcohol, falling promptly with any marked reduction of the latter from any cause and as quickly rising when the consumption of alcoholic beverage was resumed. Nevertheless, there are still many pathologists who call attention to the fact that atrophic cirrhosis can and does occur in total abstainers and who insist that alcohol per se plays no part in its production.

From a pathologic standpoint the atrophic cirrhotic liver is usually smaller than normal, as the name implies, and harder and tougher. However, especially if it is associated with fatty infiltration, as is quite frequently the case, it may be larger. Mallory [9] reported a case in which the organ weighed 3,580 Gm. The surface of the organ is irregular and nodular, the nodules varying in size from a millimeter or two to a centimeter or more in diameter but being fairly uniform in size in any given organ and separated from each other by depressions produced by scarring. The surfaces of the nodules are generally smooth, their apexes being from a millimeter or two to several millimeters above the deepest parts of the intervening depressions. The nodules, especially when their surfaces are exposed by cutting, are pale yellowish or orange, sometimes tinged with greenish bile and fairly flabby. They stand out quite sharply on the cut surfaces of the organ, being clearly delimited by the thin bands of smooth, leathery, tough intervening connective tissue.

Histologically, abnormally grouped accumulations of hepatic cells are found to be set apart from each other by interlacing bands of connective tissue, which often appears mildly inflamed. The parenchymal cells themselves show the characteristic changes. Many, often nearly all, of the cells contain fat vacuoles, and this accumulation of fat is considered by many, notably Norris,[19] to be the most characteristic lesion of the liver in chronic alcoholism. In many of these fat-containing cells, more rarely in those containing no fat, are found the peculiar irregular acidophilic hyaline accumulations which have been described at length by Mallory [9] and which are considered by many to be the typical lesion of alcoholic cirrhosis. In Mallory's opinion, it is the excessive accumulation of this hyaline substance which ultimately destroys the hepatic cell and leads in the course of years to the final shrinkage of the organ and the replacement of much of the hepatic parenchyma by fibrous tissue. Connor and his collaborators found, in addition to marked fatty infiltration, similar hyaline degenerative changes in the liver cells of most of their animals. It is our opinion, therefore, that in man fatty infiltration and degeneration, the accumulation of a hyaline substance in the hepatic

19. Norris, C.: Bull. New York Acad. Med. **4**:690, 1928.

cell cytoplasm and ultimately, in some patients at least, actual atrophic cirrhosis of the liver can result from chronic alcoholism.

On the heart and the vascular system alcohol per se has little definite effect. Fatty infiltration of the myocardium and hypertrophy and dilatation of the heart have been described in obese addicts to alcoholic liquors, especially beer drinkers, and the so-called "Munich beer heart" has been described by many workers. But such changes are in no way peculiar to those who suffer from alcoholism. Lazy, gluttonous persons of sedentary habits, even though abstainers, may show such changes. The imbibing of large amounts of liquor, especially beer or ale, may merely accentuate the process. Indeed, some clinicians, notably Helwig,[20] believe that alcohol not only is not of etiologic significance in any type of heart disease but can actually be utilized as a food by cardiac muscle and can be employed therapeutically in certain cases.

Arteriosclerosis was once considered to be a result of the excessive use of alcohol, and Welch [3] accepted it as such. Cabot,[21] Leary,[5] Ruffer,[22] Wells [23] and many others, however, have quite convincingly done away with the tenability of this theory. Indeed, Leary,[5] Martland [2] and others, as previously noted, have called attention to the fact that in many drinkers there is less arteriosclerosis than in abstainers of the same general age group. Does alcohol, they have asked, actually act to prevent arteriosclerosis because it is a solvent of cholesterol? Whether or not it can play a part in preventing arteriosclerosis or in delaying its development is not known with definiteness at the present time. From a clinical point of view such a hypothesis seems not only untenable but actually fantastic. That alcohol does not produce arteriosclerosis, however, seems to be definitely proved on the basis of the evidence now available.

The effect of alcohol on the kidneys, like its effect on the liver, has been the subject of much discussion, argumentation and experimentation. Welch [3] expressed the opinion that alcohol in excess was injurious to the kidneys, quoting the observations of Glaser, who found leukocytes and casts in the urine after a single alcoholic excess, and of Strumpell, who regarded renal disorders as the most common of all the pathologic effects of alcoholism. MacNider,[24] MacNider and Donnelly [25] and others, however, found that alcohol was only slightly and transiently nephrotoxic to normal dogs whereas dogs with renal lesions already present were more susceptible to its deleterious effect. An alcoholic

20. Helwig, F. C.: J. Missouri M. A. **37**:204, 1940.
21. Cabot, R. C.: J. A. M. A. **43**:774, 1904.
22. Ruffer, A., cited by Martland.[2]
23. Wells, H. G., in discussion on Hultgren.[27]
24. MacNider, W. deB.: J. Pharmacol. & Exper. Therap. **26**:97, 1925.
25. MacNider, W. deB., and Donnelly, G. L.: Proc. Soc. Exper. Biol. & Med. **29**:581, 1932.

beverage made in the laboratory by fermenting with yeast and then distilling a mixture of corn meal and sugar or corn meal and molasses did produce changes in the kidneys, but these were considered to be due to impurities in the crude beverage, not to alcohol. Hanzlik [26] found no changes in the kidneys of pigeons after long periods—thirteen months to two years—of chronic alcoholism. Hultgren [27] showed that alcohol, taken daily, is not a cause of chronic renal disease. Bright's disease in a person with chronic alcoholism is due to some other toxic agent. Hultgren considered that the tissues which excrete alcohol, namely, the lungs and the kidneys, were less affected than the digestive and nervous systems. The opinion of the majority of pathologists today is in accord with the view expressed by this investigator, namely, that the kidneys show no characteristic lesions in chronic alcoholism.

The effect of alcohol on the blood, on the blood-forming organs and on leukocytes has been studied by a number of workers. As far as I am aware, no specific effect of alcohol on either the erythrocytes or the hemopoietic centers in the bone marrow has been demonstrated or suggested. That alcohol does affect the opsonic power of the blood serum, however, has been shown by several workers, notably Rubin,[28] who found that 1 part of alcohol in 500 parts of blood serum reduced the serum's phagocytic action on cocci by 44 per cent. Stewart [29] found a similar drop in the opsonic power of blood serum when small amounts of port wine, about 2 ounces (58 cc.), had been taken. He also found that Peruna, the old family remedy, when taken in doses of about 2 ounces caused a fall in opsonic power of the blood serum of about 40 to 90 per cent. In somewhat similar experiments on rats, Klepser and Nungester [30] observed that deep intoxication resulted in a loss of positive chemotaxis on the part of neutrophils toward pneumococci and that intoxicated animals were therefore more susceptible to pneumococcic infection than were normal rats.

Probably as a result of such influences on the defensive mechanisms of the body, resistance to infections in persons with chronic alcoholism is lower than in normal or abstaining persons of the same age group. Parkinson [31] and Langmead and Hunt [32] have discussed this problem in

26. Hanzlik, P. J.: J. Pharm. **43**:339, 1931.

27. Hultgren, J. F.: J. A. M. A. **55**:279, 1910.

28. Rubin, G.: J. A. M. A. **48**:1432, 1907.

29. Stewart, C. E.: Mod. Med., Battle Creek **16**:241, 1907.

30. Klepser, R. G., and Nungester, W. J.: J. Infect. Dis. **65**:196, 1939.

31. Parkinson, P. R.: Lancet **2**:1580, 1909.

32. Langmead, F. S., and Hunt, T. C.: Alcohol and the Body's Resistance to Infection, in Emerson, H.: Alcohol and Man, New York, The Macmillan Company, 1935, pp. 180-200.

some detail. Pickrell [33] showed that alcoholic intoxication in rabbits destroyed their resistance to pneumococcic infection and deprived immune animals of their immunity. The effect, in his opinion, was chiefly on the smaller blood vessels, which failed to react normally to the presence of injurious agents in their vicinity. Capps and Coleman [34] reported a study of the effect of alcohol on the prognosis of pneumonia in the Cook County Hospital. So much higher was the mortality from this disease in alcoholic patients that they estimated that, of a total of 3,422 patients with lobar pneumonia studied, approximately 439 died who might otherwise have survived.

It is on the central and peripheral nervous systems that chronic alcoholism has a profound effect. By some, notably Martland,[2] this effect has been considered to be due in all probability to its action on fatty substances. To the absence of fatty substances in the kidneys they likewise attributed the lack of serious damage to these organs. Because the major manifestations of alcoholic damage to the brain are clinical, a detailed discussion of this subject is not within the scope of this paper. Nevertheless I should like to mention the few recognizable morphologic changes which may occur in the brain and the peripheral nerves.

Such changes when compared with the severity of the clinical syndrome are surprisingly slight. Moreover, since death from chronic alcoholism alone is uncommon, the changes discovered are often complicated by lesions due to other or associated causes, and the part which alcohol played or did not play in their production cannot be accurately judged. Among the structural alterations which are most commonly found are: edema of the pia-arachnoid, often with a cloudiness of this membrane which indicates a mild inflammatory process and often slight fibrosis; congestion of the meningeal veins; sometimes actual meningeal or subdural hemorrhages which, more often than not, have resulted from trauma; edema and congestion of the brain tissue itself. These changes, while common in persons with chronic alcoholism, are not pathognomonic and may be found in other conditions, such as arteriosclerosis, syphilis of the central nervous system and senility.

Internal hemorrhagic pachymeningitis is sometimes found, and it may be the actual cause of death of the patient. In general, such a lesion cannot be attributed to intoxication alone. The lesion is characterized by the presence of a thick layer of clotted, often partly organized blood which lies between the dura mater and the arachnoid, usually adherent to the outer membrane because of the attempt by fibroblasts from the dura to invade and organize it. When cut through, the clot often has a

33. Pickrell, K. L.: Proc. Soc. Exper. Biol. & Med. **38**:265, 1938; Bull. Johns Hopkins Hosp. **63**:238, 1938.

34. Capps, J. A., and Coleman, G. H.: J. A. M. A. **80**:750, 1923.

laminated appearance, owing to the fact that successive hemorrhages may have occurred, each manifesting a different stage in the process of organization.

The cerebral tissues, unless atrophic from senile changes or vascular lesions in the development of which alcohol plays no part, show little other than the edema and congestion already mentioned. Sometimes, too, the ventricles may be moderately distended with fluid. Whether or not one can still attribute to alcoholic poisoning the cerebral atrophy, granular ependymitis and gliosis described by older pathologists, notably Welch,[3] I strongly doubt. Even by employing delicate histologic technics, it has not been possible to demonstrate cytologic lesions which could be attributed to alcohol. The alterations which are found in the brains of patients suffering from Wernicke's disease and Korsakoff's psychosis are due not to alcohol but to the accompanying nutritional deficiency.

Physiologically, it can be shown that alcohol affects the brain very definitely. Its action on this organ, according to Himwich,[35] Dodge and Benedict [36] and others, is that of a depressant, and under its influence, even though the subject feels stimulated and alert, his functional accuracy and efficiency are diminished. Moreover, as Himwich and collaborators [37] have recently shown, the ingestion of fairly large amounts of alcohol is followed by acidosis. This, in their opinion, is due in part to the depressant effect of alcohol on the respiratory center, which results in a decrease in respiratory volume. Inadequate pulmonary ventilation follows, with resultant accumulation of carbon dioxide, an acid, in the blood. At the same time, oxidation in the cells of the body is diminished, and there is consequent accumulation of another acid, lactic acid, in the blood, still further increasing the acidosis.

Such abnormalities, however, even though they manifest themselves physiologically and chemically in such a manner as to be detectable by studies made on the subject during life, produce no recognizable concomitant morphologic alterations of the nerve cells, at least as far as studies up to the present time have disclosed.

The effects of alcohol on the peripheral nerves are too well known to need mention, and will not be considered in any great detail here. Suffice it to say that from a clinical point of view the neuritis which has long been known to be associated with chronic alcoholism has many points of similarity with that which occurs in the disease beriberi, without

35. Himwich, H. E.: Physiological Action of Alcohol, in Emerson, H.: Alcohol and Man, New York, The Macmillan Company, 1935, pp. 1-23.

36. Dodge, R., and Benedict, F. G.: Psychological Effects of Alcohol, Publication 232, Carnegie Institution of Washington, 1915.

37. Himwich, H. E.; Nahum, L. H.; Rakieten, N.; Fazikas, J. F., and DuBois, D.: Am. J. Physiol. **101**:57, 1932. Himwich, H. E.; Nahum, L. H.; Rakieten, N.; Fazikas, J. F.; DuBois, D., and Gildea, E. F.: J. A. M. A. **100**:651, 1933.

alcoholism. Since the work of Shattuck,[38] in 1928, when the suggestion was made that neuritis in man might result from a dietary deficiency, more and more evidence has accumulated to show that the neuritis which is associated with alcoholism is not due to the alcohol itself but to the inadequate intake of vitamins during the periods of inebriation. Apparently, then, a vitamin deficiency, more particularly a deficiency of vitamin B_1, is responsible for the neuritis of chronic alcoholism. It appears, therefore, that the role which alcohol was once believed to play as a direct cause of a neurologic disturbance is now, as a result of recent studies, to be assigned to another agent. The pathologic changes which occur are degenerative. The myelin sheaths of the affected nerves disintegrate with the liberation of lipid droplets, which are subsequently removed by macrophages. The axis-cylinders persist usually for some time but ultimately become irregular and swollen and finally, like the sheaths, disintegrate and disappear.

The complications which occur in association with alcoholism are usually found in the stage of acute alcoholism. In general, they are traumatic in nature, although strictly medical complications may occur.

The exhaustive studies of alcoholism by Moore and Gray[39] in the Boston City Hospital showed that surgical complications were present in 14,668 of 16,054 alcoholic patients admitted to the emergency department of the hospital during the years from 1923 to 1938. These complications consisted of all varieties of injuries from the simplest abrasion judged to have been obtained because of the state of drunkenness to severe and fatal complications, such as fractures of the skull and concussion. In general, the commonest site of injury was the head, 10,494 of the male and 380 of the female patients suffering from some sort of injury to the head. The next most common sites of injury were the extremities, 2,990 men and 257 women suffering from injuries of these parts. The injuries most often found were abrasions, contusions, lacerations, strains, sprains and fractures. Epistaxis, concussion of the brain and immersion were also fairly common.

Medical complications occurred in only 993 of the 16,054 patients. Of these, neurologic disturbances, such as delirium tremens and cerebral edema, occurred in 517, more than half the total. Gastrointestinal disturbances, chiefly acute gastritis, occurred in 240 more, while cardiovascular disturbances, malnutrition, effects of poverty, effects of exposure, infection of the respiratory tract and poisoning occurred in 349 patients.

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38. Shattuck, G. C.: Am. J. Trop. Med. **8**:539, 1928.

39. Moore, M., and Gray, M. G.: New England J. Med. **221**:55, 1939; **221**: 58, 1939.

Moore and Gray reported that in this entire series 75 patients—72 men and 3 women—died. All but 7 of these died on the first or second day in the hospital. The commonest cause of death was fracture of the skull or concussion of the brain, occurring in 20 patients. Head injury occurred in 17, cerebral edema in 6, cardiac disease in 10, delirium tremens in 4 and acute pneumonia in 2.

Other common causes of death include suffocation from aspiration of regurgitated gastric contents, from obstruction of the glottis or the larynx with some foreign body, most commonly a large piece of meat (Hirsch [40]), or from aspiration of an alcoholic beverage by a patient in a stupid or irrational state.

As I have noted previously, the person with chronic alcoholism is apt to be less resistant to infection than the abstainer, and this on the basis of fairly definite evidence of a specific effect of alcohol on leukocytes and the defense mechanism as it concerns smaller blood vessels and immune substances in the blood serum. For this reason, deaths from intercurrent infections, especially acute pneumonia, are common. In such cases there may be little or no evidence of the specific effect of alcohol on the various tissues of the body unless it be the liver, where the long term action of the beverage may leave its mark.

In conclusion, then, it may be said that the effect of chronic and acute alcoholism on the organs and tissues of the body is not, with the exception perhaps of the liver, specific for alcohol per se. In general, the changes which occur are those of low grade chronic irritation, chiefly mild inflammation and possibly atrophy of the gastric mucosa, edema and congestion of the brain and its coverings, and possible minor alterations in the kidneys. The debatable lesion of cirrhosis of the liver is the only one in the causation of which alcohol may prove to play more than a minor role. These minor morphologic alterations are in strong contrast to the severe clinical manifestations of alcoholism and suggest that the effect of alcohol, like that of other poisons, is primarily physiologic and chemical, not one which manifests itself in recognizable structural changes. If the various complications which may be associated with alcoholism and whose onset or origin may be traced directly or indirectly to the alcoholic state are considered as a part of the pathologic process, the picture becomes immeasurably more complex. It then extends beyond the limit of this presentation.

40. Hirsch, C.: Laryngoscope **50**:331, 1940.

Notes and News

University News, Promotions, Etc.—William C. Von Glahn, associate professor of pathology in Columbia University, has been appointed head of the department of pathology and laboratories at Bellevue Hospital, New York, and professor of pathology in the New York University College of Medicine.

In George Washington University, Washington, D. C., Richard E. Kelso has been appointed instructor in pathology.

Richard W. Linton, assistant professor of pathology, Cornell University Medical College, New York, has become a member of the staff of the Biochemical Research Foundation, Newark, N. J.

It is reported that Herbert Lund, research fellow in legal medicine at Harvard Medical School, has been appointed pathologist to the Cleveland City Hospital, succeeding Herbert S. Reichle.

Deaths.—Frank Burr Mallory, professor emeritus of pathology in Harvard Medical School and consulting pathologist of the Boston City Hospital, died on September 27, aged 78. A sketch of Dr. Mallory will be published later.

Joseph Rigney D'Aunoy, professor of pathology and bacteriologist at the Louisiana State University School of Medicine, died September 17, at the age of 51 years.

Awards.—Edgar Allen, professor of anatomy in Yale University, has been awarded the Baly Medal of the Royal College of Physicians, London, for his work on estrogens.

The Theobald Smith Award in the Medical Sciences of the American Association for the Advancement of Science has been presented to Herald R. Cox, principal bacteriologist in the United States Public Health Service, for his work on virus diseases.

John H. Lawrence, professor of medicine in the University of California, has been awarded the medal of the American Roentgen Ray Society for his work on artificially radiocative substances.

At its meeting June 1, 2 and 3, 1942, in Atlanta, Ga., the American Association for the Study of Goiter will again award the Van Meter Prize of $300 for investigative work, clinical or experimental, on thyroid problems. The corresponding secretary, Dr. J. C. Davison, 478 Peachtree Street, Atlanta, will be glad to furnish further information in regard to this award. All reports to be considered for the award must be in his hands before April 1, 1942.

Louis F. Fieser, Harvard University, has been awarded the Katherine Berkan Judd $1,000 prize of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, in recognition of "his outstanding contribution in the proof of the active and inactive positions in the molecules of the chemical carcinogens."

Society News.—The Society of American Bacteriologists will hold its annual meeting on December 29, 30 and 31 at the Lord Baltimore Hotel, Baltimore.

Book Reviews

Pathology of the Oral Cavity. Lester Richard Cahn, D.D.S.; associate professor of dentistry (oral pathology), Columbia University; Fellow of the American Association for the Advancement of Science; Fellow of the New York Academy of Dentistry; Associate Fellow of the New York Academy of Medicine. Pp. 240, with 165 illustrations. Price $5.50. Baltimore: The Williams & Wilkins Company, 1941.

Oral Pathology: A Histological, Roentgenological and Clinical Study of the Diseases of the Teeth, Jaws and Mouth. Kurt H. Thoma, D.M.D., professor of oral surgery, Harvard University, Boston. Cloth. Pp. 1306, with 1370 illustrations. Price $15. St. Louis: C. V. Mosby Company, 1941.

Cahn's book treats of the more common diseases of the oral structures. The descriptions are brief and in the main well illustrated. There are colored drawings of glossitis in vitamin B deficiency, Fordyce's disease, melanotic pigmentation, acute pericoronal infection, leukoplakia, ranula and melanoma of the gum. The book will be of service as an introductory guide. The chapters on tumors are least satisfactory. Among tumors are included hematoma, granuloma and retention cysts. On pages 229 and 230 one reads: "The chief characteristics of all these tumors (transitional cell carcinoma, lymph-epithelioma, lymphosarcoma) is that they are composed of small, round, undifferentiated cells that bear no resemblance to normal squamous epithelium. Also they are highly sensitive to radiation. The first two arise from the covering epithelium. The lymphosarcoma originates from the lymphoid elements of the oropharynx. However, it may be impossible to differentiate any of the three under the microscope. Lymph gland involvement in all three types is early, and often extensive; and in spite of the extreme radiosensitivity of these tumors metastasis is widespread. A fatal issue is inevitable." As a whole this statement is, to say the least, confusing, and the last sentence is utterly misleading.

Thoma's massive volume also "deals with the pathology of the teeth, the jaws, and the oral mucosa" but on a comprehensive scale and with special regard to the relations between oral diseases and somatic disturbances. An outline of the contents will indicate the scope of the book, which falls into twelve parts.

The first part discusses the general pathology of oral diseases, mainly from the standpoint of experimental work. The hereditary, endocrine and nutritional influences on the development of the teeth and the jaws are considered. The next two parts are concerned with developmental anomalies of the teeth and the head. There are chapters on developmental errors of dentition, on deviations in the form and structure of the teeth, on malformations of the face and jaws, on modifications of growth by local and by somatic factors and on malocclusion of the teeth. Parts 4 and 5 cover functional changes of the teeth under various conditions and injuries of the teeth. Odontitis, periodontal diseases and extension of odontogenic infection are the subjects of parts 6, 7 and 8. The chapters on odontitis (dental caries, pulp involvement, dentoalveolar abscess) extend over some 150 pages. Parts 9 and 10 deal with diseases of the jaws and with tumors of the jaws and of the oral mucosa. The next part takes up diseases of the oral mucosa, lips and tongue, and the last part, diseases of the salivary and mucous glands.

In the preface the book is referred to as a textbook, but it is rather an encyclopedia or system of oral pathology. Each part is, in fact, a more or less monographic presentation or review, sometimes rather hurried, of present knowledge of the part of oral disease with which it deals. Helpful bibliographies are appended to the chapters. In spite of a tendency to discursiveness, loose organization and the introduction in detail of more or less extraneous matter, the book

is a rich source of informtion on all aspects of oral disease and should be available in dental and medical libraries.

There are 1,370 illustrations, 137 of them in color and on inserts. The black and white illustrations are as a rule well chosen and instructive. Some of them are worthless, however, and there are examples of needlessly repetitious illustration of familiar appearances. Probably most of the roentgen films shown can be classed as good, but it frequently happens that the feature of special interest is clearly seen while outlines of other details are missing. More attention should have been given to eliminating illustrations of doubtful value. This statement applies particularly to the photomicrographs in color, almost all of which suffer from lack of definite nuclear staining and differentiation (figs. 1072, 1075, 1353 are exceptions). The staining methods used in preparing the sections photographed in color are not given. The two best colored microscopic illustrations in the book are figures 2 and 1137, and these are reproductions of camera lucida drawings. The colored illustrations of gross appearances, mostly oral lesions, have much more of illustrative value than the colored photomicrographs, but here also more critical selection should have been exercised.

In case a second edition is published, the book could be greatly improved by thorough revision with condensation of the text and by a more discriminating selection of illustrative material.

Textbook of Bacteriology. Edwin O. Jordan, Ph.D., late Andrew McLeish distinguished service professor of bacteriology, University of Chicago; and William Burrows, Ph.D., assistant professor of bacteriology, University of Chicago. Thirteenth edition, revised. Pp. 731, with 170 illustrations. Price $6. Philadelphia: W. B. Saunders Company, 1941.

It is a satisfaction to one who has appreciated Jordan's "Bacteriology" through all of its many editions to find that the mantle of the late senior author has fallen on capable shoulders. This new (thirteenth) edition has been largely rewritten, with the elimination of certain chapters in highly specialized fields, such as soil and dairy bacteriology, and the title has been appropriately changed to "Textbook of Bacteriology"; the book has always had a medical bent and it never was a "general bacteriology" in any true sense of that term.

Two outstanding improvements will be found in the excellent presentation of bacterial physiology and of the filtrable viruses, to each of which more space has been allotted. Would that the chapters on immunity and its applications had been equally strengthened! Isohemagglutinins are merely mentioned and allergic phenomena dismissed all too casually.

In a number of the discussions the author has used tables to indicate the physiologic reactions of the members of the group of organisms; this method could be used consistently throughout to the great advantage of the beginning student and with a saving of many pages. The term "diagnosis" is not used as a paragraph heading in this book, and although the appropriate procedures are usually given, they are difficult to find at times, and more stress and more definite presentation of the methods involved under such a section heading would, in the opinion of the reviewer, be a decided improvement, certainly for medical students.

Satisfaction is expressed that the subject of the protozoa has not been cut out under pressure for space, as it has been in several leading textbooks of bacteriology. In fact, following the precept and practice of that great student of disease, Theobald Smith, the reviewer would like to see the helminths, pathogenic for man, also included, as the reactions of the body to injury have much in common whatever the class into which the parasite may be placed. The personnel of the laboratory from which this book stems is admirably fitted to produce a major text covering all the parasites of man.

One more minor "carping" from the critic is this: The author pungently characterizes the chaotic condition of classification and nomenclature in bacteriology and then, to one's regret, prints the latest Bergey taxonomic anomaly at the head

of the chapter on streptococci, placing these organisms in the same family with Bacillus bulgaricus and Bacillus acidophilus, largely because they all ferment carbohydrates with the production of lactic acid. One would think that all animals eliminating urea might almost equally well be placed in the same family.

The typography is excellent and the selection of material and illustrations expert. Students of biology and of medicine will continue to profit by its use.

Biological Symposia on Muscle. Editor: Wallace O. Fenn, M.D., professor of physiology, The University of Rochester School of Medicine and Dentistry, New York. Cloth. Pp. 370, with 82 illustrations. Price $3. Lancaster, Pa.: The Jaques Cattell Press, 1941.

This book is an outcome of a symposium on muscle organized by Wallace O. Fenn at the request of the American Physiological Society for the latter's annual meeting at New Orleans in April 1940. It contains fifteen original articles on subjects immediately related to the contractile mechanism of muscle.

The following list of the contributing physiologists with the titles of their papers gives a good idea of the contents: Wallace O. Fenn, "Introduction to Muscle Physiology"; Robert W. Ramsey and Sibyl F. Street, "Muscle Function as Studied in Single Muscle Fibers"; Frederick H. Pratt, "Muscle and the Heart's Motto"; Henry A. Blair, "Muscle Excitability"; Emil Bozler, with discussion by A. S. Gilson Jr., "Action Potentials and Conduction of Excitation in Muscle"; Arturo Rosenblueth, "Conduction in Smooth Muscles"; T. P. Feng, "The Local Activity Around the Skeletal N-M Junctions Produced by Nerve Impulses"; Allan C. Young, "Action Potentials of Skeletal Muscle"; Dugald E. S. Brown, "The Regulation of Energy Exchange in Contracting Muscle"; Herbert Elftman, "The Action of Muscles in the Body"; Francis O. Schmitt, "Changes During Muscle Contraction as Related to the Crystalline Pattern"; Otto Meyerhof, "The Significance of Oxidations for Muscular Contraction"; C. A. G. Wiersma, "The Efferent Innervation of Musele"; G. D. Gammon, R. L. Masland and A. M. Harvey, "On the Nature of Certain Diseases of the Voluntary Muscles"; Robert B. Dean, "Theories of Electrolyte Equilibrium in Muscle"; J. C. Eccles, B. Katz and S. W. Kuffler, "Electric Potential Changes Accompanying Neuromuscular Transmission."

Each article is an original contribution placed in historic perspective. The introduction to muscle physiology is an excellent one and should be read by the scientist and the clinician interested in muscle function. The multiple methods employed in the study of muscle are revealed by the research on tension, heat, action potential, optical changes, microscopic structure, roentgen ray diffraction patterns, liquid crystals, electrolytes, oxidation, muscle mechanics and disease.

The following picturesque and clear statements of Fenn are characteristic in the writings of the selected contributors: "The muscle is a self-cocking explosive machine with a convenient trigger. The forces developed in a muscle 'explosion' are of amazing magnitude. Most of the principles of muscle physiology which are usually taught in the class room by fussy experiments on moribund frog muscle are better exemplified by experiments on man."

Confidence is expressed in this book that a complete understanding of the actual mechanism of muscle contraction is not beyond reach, provided the future economic order allows pursuit of the truth and encourages "a type of research which is without immediate promise of cash return or military advantage."

Books Received

HANDBOOK OF COMMUNICABLE DISEASES. Franklin H. Top, A.B., M.D., M.P.H., director, Division of Communicable Diseases and Epidemiology, Herman Kiefer Hospital and Detroit Department of Health; associate professor of preventive medicine and public health, Wayne University College of Medicine; special lecturer in communicable diseases and epidemiology, University of Michigan; major, Medical Reserve Corps, United States Army; and collaborators. Pp. 682, with 73 text illustrations and 10 color plates. Price $7.50. St. Louis: C. V. Mosby Company, 1941.

SYNOPSIS OF APPLIED PATHOLOGICAL CHEMISTRY. Jerome E. Andes, M.S., Ph.D., M.D., F.A.C.P., director of department of health and medical advisor, University of Arizona, Tucson; formerly assistant professor of pathology and clinical pathology, West Virginia University Medical School; and A. G. Eaton, B.S., M.A., Ph.D., assistant professor of physiology, Louisiana State University School of Medicine, New Orleans. Pp. 428, with 23 illustrations. Price $4. St. Louis: C. V. Mosby Company, 1941.

THE ROCKEFELLER FOUNDATION, INTERNATIONAL HEALTH DIVISION, ANNUAL REPORT, 1940. New York: Rockefeller Foundation, 1941.

SURGERY OF THE HEART. E. S. J. King, M.D., M.S., D.Sc. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Major A.A.M.C., Honorary Surgeon to Outpatients, Royal Melbourne Hospital; Jacksonian Prizeman, Royal College of Surgeons; Sometime Stewart and Senior Lecturer in Pathology and Stewart Scholar in Surgery, University of Melbourne. Pp. 728, with 268 figures. Price $13.50. Baltimore: The Williams & Wilkins Company, 1941.

IMMUNITY AGAINST ANIMAL PARASITES. James T. Culbertson, assistant professor of bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 274, with 4 figures. Price $3.50. New York: Columbia University Press, 1941.